EXHIBIT A

EXHIBIT A

GENERAL LIABILITY EXPERT: SALIL KHANDWALA

Defense Expert Name	Plaintiff Name	Case No.
Khandwala, Salil		
Khandwala, Salil	Schomer, Margaret	2:12-cv-01497
Khandwala, Salil	Chase, Alvette	2:12-cv-01533
Khandwala, Salil	Lindberg, Patricia	2:12-cv-01637
Khandwala, Salil	Smallwood, Nancy	2:12-cv-01662
Khandwala, Salil	Meyer, Linda	2:12-cv-01705
Khandwala, Salil	Lambert, Corrie Ann	2:12-cv-02183
Khandwala, Salil	Pieper, Laura	2:12-cv-02189

EXHIBIT B

UNITED STATES DISTRICT COURT

SOUTHERN DISTRICT OF WEST VIRGINIA

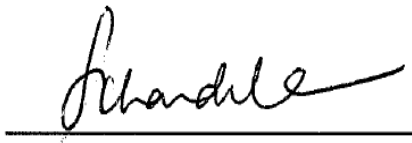
CHARLESTON DIVISION

IN RE: ETHICON, INC., **PELVIC REPAIR SYSTEM** **PRODUCTS LIABILITY LITIGATION**	**Master File No. 2:12-MD-02327** **MDL 2327** **JOSEPH R. GOODWIN** **U.S. DISTRICT JUDGE**

DEFENSE EXPERT GENERAL REPORT

OF SALIL KHANDWALA, M.D.

Prepared by



Salil Khandwala, M.D.

June 3, 2016

GYNECARE RETROPUBIC TVT and TRANSOBTURATOR TVT-O SUBURETHRAL SLING

The following is a designation of my expert opinions for the general report on TVT and TVT-O . All opinions held by me are to a reasonable degree of medical certainty and I reserve the right to supplement or modify my expert opinion based on the discovery, disclosure and timely provision of new findings. My opinions in this report are based on my critical review of TVT and TVT-O that I have implanted in hundreds of women, my extensive clinical experience implanting of over a thousand polypropylene midurethral slings, my education, subspecialty training, analysis of my own clinical trials, reading of the peer-reviewed medical literature, discussions with colleagues, my assessment of the anatomy and the function of devices in clinical surgery, and my Professional Education and experience in teaching the procedure in cadaver labs and on real surgical case proctorships. Based on all of this experience, I can testify up to a reasonable degree of medical certainty.

My *curriculum vitae* is attached, which includes a list of publications I have authored especially in the field of midurethral slings. A complete list of materials reviewed in forming my opinions is attached.

My hourly rate is $500.00 per hour. In the last four years, I have testified in the following cases:

Dina Sanders Bennett v. Ethicon, Inc., et al.; In The United States District Court For The Southern District Of West Virginia Charleston Division; Case No. 2:12-cv-00497

Pamela Free v. Ethicon Inc. et al.; In The United States District Court For The Southern District Of West Virginia Charleston Division; Case No. 2:12-cv-00423

Barbara Kaiser et al. v. Ethicon, Inc. et al.; In The United States District Court For The Southern District Of West Virginia Charleston Division;Case No. 2:12-0887

Beverly Kivel v. Ethicon, Inc., et al.; In The United States District Court For The Southern District Of West Virginia Charleston Division; Case No. 2:12-cv-0-591

Shirley Walker, et al. v. Ethicon, Inc., et al.;In The United States District Court For The Southern District Of West Virginia Charleston Division; Case No. 2:12-cv-00873

Brenda Riddell et al. v. Ethicon, Inc. et al. .;In The United States District Court For The Southern District Of West Virginia Charleston Division; Case No. 2:12-cv-00547

I. BACKGROUND AND EDUCATION

I received the Bachelor of Medicine and Surgery (M.B.B.S) in 1985 from the University of Bombay, India, a residency in Obstetrics and Gynecology (M.D.- Ob Gyn) in 1990 from Bombay, India and from the Greater Baltimore Medical Center in 1997, a fellowship in Operative Laparoscopy and Hysterectomy in 1993 from the University of Clermont Ferrand, France , and a fellowship in Urogynecology, Reconstructive Pelvic Surgery and Operative

Endoscopy in 1998 from the Greater Baltimore Medical Center/University of Maryland. I am board-certified in obstetrics and gynecology.

I am board-certified in FPMRS. I, in fact, was part of the first group that got certified once this subspecialty became credentialed.

I have taught as an Assistant Professor in the Division of Urogynecology and Pelvic Reconstruction Surgery department at the University of Maryland from 1998-2002. I am currently an Associate Professor in the department of Obstetrics and Gynecology at Wayne State University School of Medicine.

I am currently the Director of Female Pelvic Medicine and Reconstructive Surgery at Beaumont Hospital System - Oakwood campus in Dearborn, Michigan. I have been in the practice treating women's health issues since 2000. Specifically, I have treated women with Urinary Incontinence and Pelvic Organ Prolapse since 1997. I, earlier in my career, used the Burch colposuspension (both laparoscopic and laparotomy/open) and fascia lata and rectus fascial slings to treat SUI. Since TVT and mid-urethral slings came to the market they have been my choice for SUI repair especially after reading the extensive literature on this, notably the Hilton and Ward study(1).

I have performed over 2000 SUI surgeries, and have performed approximately 100 TVT slings, 400 TVT-O slings, 300 TVT SECUR procedures and several other midurethral sling operations. I continue to perform these procedures and instead of the TVT SECUR, I perform a similar single incision sling. The only reason I am not performing the TVT SECUR is because it has been removed from the market to my chagrin as I was enjoying excellent personal results. With regards to pelvic organ prolapse (POP) I have been managing this condition since 1997. I have used the following methods to repair POP: native tissue repairs including fascial plications such as anterior/posterior repairs, paravaginal repairs, McCall culdoplasty, sacrospinous ligament suspension, abdominal sacrocolpopexy, uterosacral ligament suspension, colpocleisis. I have also performed augmented prolapse surgery using the IVS Tunneller system, Prolift system, the Prolift + M system, the American Medical System (AMS) Elevate system, the Exair (Coloplast) system, the Restorelle system. I spend 90% of my time taking care of women with issues of the pelvic floor mainly, SUI and POP repair.

I am an investigator with the Urinary Incontinence Treatment Network (UITN) and the Pelvic Floor Disorders Network (PFDN)- two pivotal divisions involved with Female Pelvic Floor conditions at the National Institute of Health (NIH).

As part of the Urinary Incontinence Treatment Network, I was a co-investigator of several keystone sling projects. The first one was the SISTr project that compared Burch colposuspension to the fascial sling procedure. I was also part of a multicenter group who designed, implemented and published the largest US comparative effectiveness trial comparing

transobturator midurethral sling to the gold standard retropubic midurethral sling (the TOMUS trial). This landmark study showed the efficacy and safety of both suburethral slings.

I have also taught courses in female pelvic surgery domestically and also travelled nternationally to France, Belgium and India to teach these surgical procedures.

I have conducted several clinical trials of my own and have several papers published especially in the field of urinary incontinence and genital organ prolapse. I have been part of single center studies, multi-centric studies and also international collaborative trials.

II. Board Certification:

Board certification is a voluntary process that demonstrates a physician's expertise in a particular specialty. In addition, the American Board of Medical Specialties [ABMS (parent board to ABOG and ABU)] requires that all certified physicians engage in on-going maintenance of certification to ensure that they stay current of advances in the evaluation and treatment of patients by that specialty.

The ABMS officially approved the specialty of **Female Pelvic Medicine and Reconstructive Surgery** in the spring of 2011. In so doing, ABMS acknowledged that care for women with complex pelvic floor disorders (such as urinary and fecal incontinence, and pelvic organ prolapse) requires subspecialty training and certification beyond the training acquired by a general obstetrician-gynecologist or a general urologist. In June of 2013, the American Board of Obstetrics and Gynecology and the American Board of Urology certified the first individual physicians. I was part of that group to be certified in FPMRS at the first attempt.

I am a fellow of the American College of Obstetrics and Gynecology (FACOG). I am also a member of the American Urogynecologic Society (AUGS).

TEACHING EXPERIENCE

I have trained over 100 Obstetrics and Gynecology residents and two Female Pelvic Medicine and Reconstructive Surgery (FPMRS) fellows. At any given time, there are 2 Ob Gyn residents working with me. I am the primary Urogynecology and FPMRS faculty for the Ob Gyn residents of Oakwood, Wayne State University, Botsford and the Genesys residency programs in Southeast Michigan. I am also the Program Director of a board-certified fellowship in FPMRS. I have had 2 FPMRS fellows. The fellow training tenure spans three years which includes basic science, clinical application and scientific research.

SEMINAL CLINICAL TRIALS THAT I WAS INVOLVED WITH AS A CO-INVESTIGATOR OF UITN

In 2000, the National Institutes of Diabetes, Digestive and Kidney Diseases (NIDDK) established the **Urinary Incontinence Treatment Network** (**UITN**), recognizing the need for

well-designed outcomes studies for urinary incontinence treatment in women as previous studies had methodological flaws and/or limitations that precluded definitive conclusions about the relative efficacy or differences in complications between procedures. (UITN. Urology 2005). Randomized controlled trials or comparative effectiveness trials are considered the best of all research designs because the act of randomizing patients to receive one intervention or the other ensures that, on average, all other factors are equal between the groups. Therefore, any significant differences in outcomes or complications between the groups can be attributed to the intervention or procedure and not to some other factor.

Stress Incontinence Surgical Treatment Efficacy Trial (SISTr): In the first trial, Burch and bladder neck slings were selected for comparison by the UITN since they were considered the 'gold standard' procedures for treating stress incontinence in the US at that time; although expert opinion existed regarding the efficacy of the procedures, no prospective comparative data was available to support or refute "expert opinions". We now have 2-year and 5-year outcome and complication data directly comparing these two procedures (2). In this multicenter RCT of 655 women followed for 24 months, success (defined as no self-reported symptoms of SUI, a negative stress test and no retreatment for SUI) was higher in the pubovaginal sling group than the Burch colposuspension group (66% versus 49%; P <0.001). However, pubovaginal slings were associated with an increased risk of UTI (48% versus 32%; P <0.001), voiding dysfunction (14% versus 2%; P <0.001), and postoperative urge incontinence requiring treatment (27% versus 20%; P = 0.04).

Extended Stress Incontinence Surgical Treatment Efficacy Trial: The extended 5 year results published by our group in 482 patients (73.6% of the initial cohort) found that continence rates had decreased substantially in both groups.

Trial of Midurethral Sling (TOMUS) study (4): This study assessed the outcome of 597 women randomized to undergo either retropubic (n = 298) or transobturator (n = 299) midurethral sling insertion. Self-reported symptoms, urinary stress tests, pad tests and retreatment rates were assessed. Objective success rates (defined as a negative provocative stress test, a negative 24 h pad test and no retreatment for SUI) at 12 months were 80.8% in the retropubic group and 77.7% in the obturator group (3% difference, 95% CI 3.6–9.6). Statistical analysis demonstrated equivalence for both procedures in objective measures; however, retropubic slings performed slightly better subjectively (62.2% versus 55.8%; 6.4% difference, 95% CI 1.6–14.3).

OVERVIEW OF STRESS URINARY INCONTINENCE

Prevalence rates

The International Continence Society (ICS) defines urinary incontinence as ‘‘the complaint of any involuntary leakage of urine,’’ providing a good clinical definition for patient evaluation(5).

A review of 21 studies by Thom(6) revealed that the pooled mean prevalence for older women was 34% for any incontinence and 12% for daily incontinence. Among middle-aged and younger adults, the pooled mean prevalence was 25%. Stress incontinence was more common in younger women, whereas urge and mixed incontinence was more common in older women. In 3 large, multinational, population-based studies, the prevalence of lower urinary tract symptoms ranged from 59.2% to 76.3%, but the prevalence of actual incontinence ranged from 9.3% to 14.8% (7-9). A large epidemiologic study of community-dwelling women in the United States by Lukacz and colleagues (10) reported that women with frequent daytime or nighttime voiding had twofold higher bother scores compared with unaffected women, and that increases in voiding frequency incrementally increased patient bother. This finding highlights the point that many women have bothersome symptoms even though they do not have incontinence.

Race and age on incontinence prevalence

Nygaard and colleagues(11) found no differences in prevalence rates between Hispanic, non-Hispanic whites, non-Hispanic blacks, and other races, whereas Dooley and colleagues (12) found that white and Mexican American women had almost double the prevalence rates for stress incontinence compared with blacks, but blacks had a higher rate of urge incontinence (11% compared with 7.5% for white and Mexican American women).

Thom and colleagues (13) specifically evaluated differences in incontinence prevalence among major race and ethnic groups in the Reproductive Risks of Incontinence Study at Kaiser (RRISK) and found that the prevalence for all types of incontinence was highest in Hispanic women (36%), followed by white (30%), black (25%) and Asian American (19%) women. Additional analysis from the RRISK suggests that incontinence is significantly associated with a decrease in quality of life, and this effect does not vary significantly by race (14).

The Establishing the Prevalence of Incontinence (EPI) study focused on comparing incontinence prevalence between white and black women. In this study, Fenner and colleagues (15) reported that a significantly higher proportion of white women reported stress incontinence compared with black women (39.2% vs 25%, respectively), whereas a greater proportion of black women reported urge incontinence compared with white women (23.8% vs 11%, respectively).

In contrast to previous studies (16), the EPI study showed that, other than race, risk factors for incontinence were similar between black and white women, including increased age, mobility

impairment, constipation, obesity, and depressive symptoms. Nygaard and colleagues reported that the prevalence of incontinence in women in the United States over the age of 80 years was 31.7% compared with women aged 40 to 59 years with a prevalence of 17.2%.

Urinary incontinence costs

The financial burden of incontinence includes direct and indirect costs. Direct costs include routine care (absorbent products and laundry), medical visits and treatments, and treatment complications or failures. Indirect costs are more difficult to estimate, and include loss of productivity and costs of paid or unpaid caregivers. Although unable to estimate a cost associated with loss of productivity, the study showed that 23% of incontinent women missed an average of 28.7 hours of work for inpatient and outpatient care. It is estimated that for stress incontinence, direct costs of medical care for surgical patients without comorbidities was $13,212 per patient (17). Subak and colleagues (18-20) provided more accurate estimates of the individual economic costs for routine incontinence care. The annual direct cost of routine care ranged from $250 to $900 in 2005 dollars per woman (18-20).

Predisposing factors

In a twin study by Altman and colleagues (21), genetic effects seemed to contribute to stress incontinence and pelvic organ prolapse, but the influence of environmental factors was also substantial.

Inciting factors

Inciting factors are those that likely could be modified, but often cannot be avoided. Although most parous women do not have pelvic floor dysfunction, one major inciting factor for pelvic floor dysfunction is childbirth. Similarly, in the RRISK cohort, Rortveit and colleagues (22) found that the risk of prolapse was significantly increased in women with 1 (odds ratio [OR] 2.8, 95% confidence interval [CI] 1.1–7.2), 2 (OR 4.1, 95% CI 1.8–9.5), and 3 or more (OR 5.3, 95% CI 2.3–12.3) vaginal deliveries compared with nulliparous women.

Promoting factors

In addition to chronically increased intra-abdominal pressure, neurogenic disease caused by obesity may place obese women at greater risk for prolapse and incontinence.(23) Obesity has been shown to be a risk factor for urinary incontinence(24). Subak and colleagues (25) conducted a randomized clinical trial, the Program to Reduce Incontinence by Diet and Exercise (PRIDE), and found that a 6-month behavioral intervention targeting weight loss reduced the frequency of self-reported episodes of urinary incontinence among overweight and obese women

compared with a control group. Burgio and colleagues (26) reported that, in incontinent women losing 18 or more BMI points after bariatric surgery, 71% regained urinary continence at 12 months.

Higher BMI has also been associated with pelvic organ prolapse. In one study, women with type 1 diabetes had a nearly twofold greater prevalence of weekly urge incontinence compared with women without diabetes (8.8% vs 4.5%) (27) . Using data from the Action for Health in Diabetes (Look AHEAD) study evaluating overweight and obese women with type 2 diabetes, Phelan and colleagues reported that weekly incontinence (27%) was reported more often than other diabetes-associated complications including retinopathy (7.5%), microalbuminuria (2.2%), and neuropathy (1.5%).

The large EPICONT study reported that former and current smoking was associated with incontinence, limited to those women who smoked 20 cigarettes a day or who had a 15 year pack history(28). It may be postulated that increased prevalence of incontinence among smokers is secondary to strong and frequent coughing, and therefore increased intra-abdominal pressure. Other theories regarding smoking and its effect on incontinence include the negative effect of smoking on estrogen, and possible interference with collagen synthesis. The prevalence of urinary incontinence in older, postmenopausal women was also found to increase almost twofold with COPD (29).

Certain medications may predispose women to pelvic floor disorders secondary to their mechanism of action (eg, by lowering bladder outlet resistance).Other drugs may predispose women secondary to side effects (eg, constipating medications or cough-inducing medications). Drugs that may predispose women to incontinence include a-adrenergics, angiotensin-converting enzyme (ACE) inhibitors, antipsychotics, benzodiazepines, and antidepressants. The role of hormone therapy on incontinence symptoms has been evaluated (30). Using data from the WHI, Hendrix and colleagues (31) reported that menopausal hormone therapy increased the incidence of all types of urinary incontinence at 1 year among women who were continent at baseline. The risk for stress incontinence was 1.87 and 2.15 fold higher for women on estrogen and progesterone therapy or estrogen therapy alone, respectively, compared with controls.

The risk for mixed incontinence was 1.49-and 1.79-fold higher for women on estrogen and progesterone therapy or estrogen therapy alone, respectively, compared with controls. In a case control study, Arya and colleagues (32) found a 2.5-fold higher risk of detrusor overactivity in women with high caffeine intake and after controlling for age and smoking.

PHYSIOLOGIC NEUROANATOMY OF URINE STORAGE AND EVACUATION

Anatomy: Bladder

The base of the bladder includes the vesical trigone, which is bounded by the two ureteral orifices and the internal urethral opening. An important distinction between the dome and the base is the type of neurotransmitter receptor that predominates. At the dome, beta-adrenergic and cholinergic receptors predominate, whereas alpha-adrenergic receptors predominate at the base and the proximal urethra. The primary cholinergic (muscarinic) receptor subtypes in the human bladder are M2 and M3. Although there are more M2 receptors, the M3 receptors predominate in the mediation of detrusor contraction.

Anatomy: Urethra

Surrounding the mucosal lining of the urethra is a submucosal layer that contains a prominent vascular plexus. This plexus is thought to contribute to the watertight closure of the urethral lumen. Adjacent to the submucosal layer lie two layers of smooth muscle: a well-developed inner longitudinal and a poorly defined outer circular layer. The most external layer of the urethral wall consists of the striated urogenital sphincter muscles (see Fig 1). This complex consists of the sphincter urethrae and two strap like bands of muscle, the urethrovaginal sphincter and compressor urethrae muscles (Fig 2).

Peripheral nervous system

The superior hypogastric plexus primarily contains sympathetic fibers from the T10 to L2 cord segments and terminates by dividing into right and left hypogastric nerves. The inferior hypogastric plexus, also known as the pelvic plexus, is formed by visceral efferents from S2 to S4, which provide the parasympathetic component by way of the pelvic nerves. The somatic component of the peripheral nervous system that is relevant to lower urinary tract function takes origin from Onuf's somatic nucleus. Onuf's nucleus, located in the ventral horn of the gray matter of S2 through S4, contains the neuronal cell bodies of the fibers that supply the striated urogenital sphincter complex.

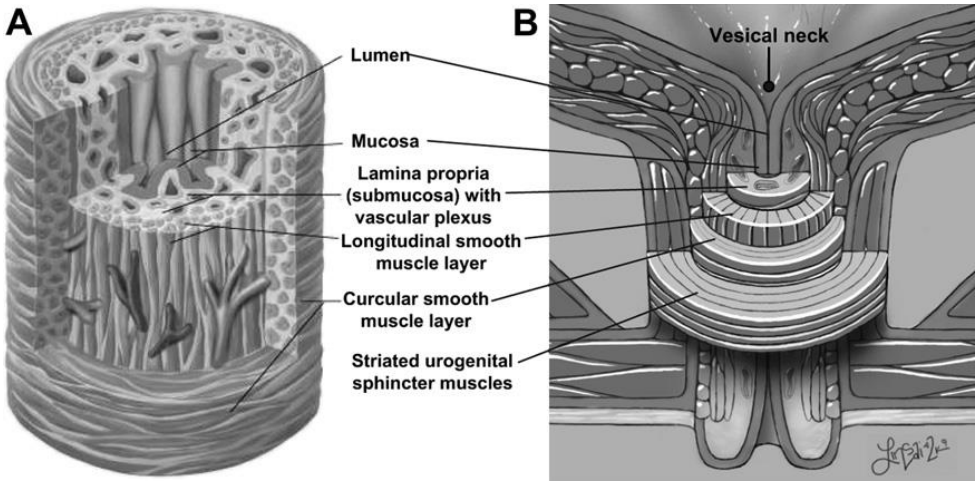


Fig. 1 Courtesy of Lindsay Oksenberg, Dallas, TX).

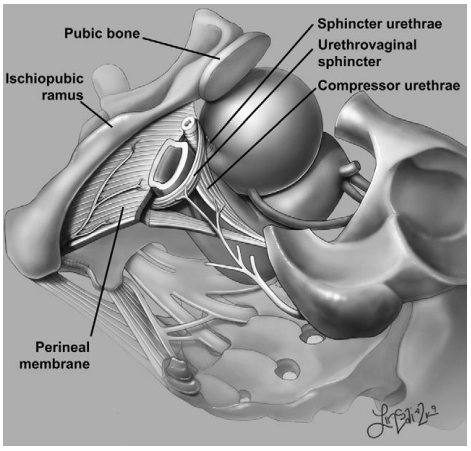


Fig 2 Striated urogenital sphincter anatomy (Courtesy of Lindsay Oksenberg, Dallas, Texas).

Neurophysiology

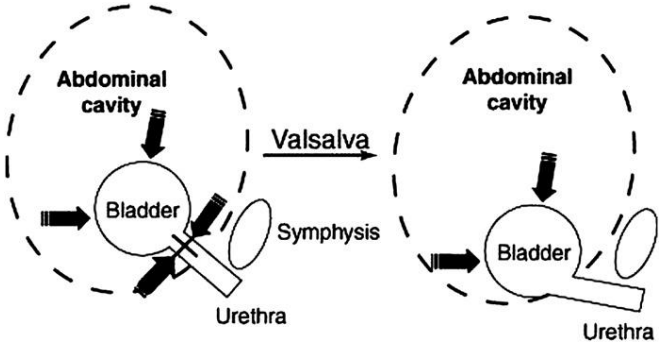
Activation of the urethral motor neurons in Onuf's nucleus results in contraction of the striated urogenital sphincter muscles by way of the pudendal nerve. Simultaneously, activation of the spinal sympathetic reflex (T11–L2) by way of the hypogastric nerves results in alpha-adrenergic contraction of urethral smooth muscle with increased tone at the vesical neck and inhibition of parasympathetic transmission, which inhibits detrusor contraction. The net effect is that urethral pressure remains greater than detrusor pressure, facilitating storage.

PATHOPHYSIOLOGY OF STRESS URINARY INCONTINENCE

Early Anatomic Theories

Kelly used his cystoscope to describe SUI, reporting that "the cystoscopic picture presents a gaping internal sphincter orifice which closes sluggishly." He attributed SUI to "vesical neck funneling," which he hypothesized was caused by loss of elasticity or normal tone of the urethral and vesical sphincter. In 1923, Bonney stated that "Incontinence appears to be due to laxity of the front part of the pubo-cervical muscle-sheet, so that it yields under sudden pressure and allows the bladder to slip down behind the symphysis pubis and the urethra to carry downwards and forwards by wheeling round the sub-pubic angle."

Pressure Transmission Theory (Enhorning)



Stress urinary incontinence: the pressure-transmission theory. (From Wai CY. Urinary incontinence. In: Schorge JO, Schaffer JI, Halvorson LM, et al, editors. Williams Gynecology. 1st edition. New York: McGraw Hill Medical; 2008. p. 518)

Enhörning developed a urethral catheter with 2 pressure transducers 5 cm apart, which permitted simultaneous measurement of vesical and urethral pressures. Using this apparatus, he showed that, in continent subjects, urethral pressure exceeded vesical pressure, both at rest and during increases in intra-abdominal pressure. He hypothesized that this equal rise in vesical and urethral pressure was due to transmission of intra-abdominal pressure to the bladder and the part of the proximal urethra above the pelvic floor. The transmitted intra-abdominal pressure maintained continence by keeping the urethral pressure differentially higher than the bladder pressure. Conversely, "In cases of stress incontinence this upper part of the urethra is often relaxed and the increase in the intra-abdominal pressure does not get transmitted to the urethra."

DeLancey's Hammock hypothesis

In 1996, DeLancey proposed a consolidated theory of SUI. Using anatomic research, he hypothesized that the pubocervical fascia provides hammock-like support for the vesical neck and thereby creates a backboard for compression of the proximal urethra during increased intra-

abdominal pressure. Loss of this support would compromise equal transmission of intraabdominal pressure. This part of DeLancey's theory combines the theories of Bonney and Enhörning. However, his theory also accounts for neuromuscular dysfunction. DeLancey's anatomic observations showed a connection of the pubocervical fascia with the insertion of the levator ani muscles at the symphysis pubis. He hypothesized that this connection with the levator ani muscles permits active elevation of the vesical neck during contraction of the levator ani muscles. This part of the theory provides a mechanism for SUI due to neuromuscular injury.

The Integral Theory

Petros and Ulmsten proposed the integral theory of urinary incontinence. This theory attempts to account for the interplay of the structures involved in female urinary continence, as well as the effects of age, hormones, and iatrogenically induced scar tissue. The investigators hypothesized that stress and urge symptoms both derive, for different reasons, from anatomic laxity in the anterior vaginal wall. The laxity may be caused by defects in the vaginal wall itself or in the ligaments and muscles that support it. According to this theory, the vaginal wall has a structural function that prevents SUI by transmitting the muscle movements involved in bladder neck opening and closing, as well as a function that prevents urgency by supporting hypothesized stretch receptors located in the proximal urethra and bladder neck.

Ideal support requires intact and healthy (1) ligaments along the lateral aspects of the urethra, termed the pubourethral ligaments; (2) anterior vaginal wall and its lateral fascial condensation; (3) arcus tendinous fascia pelvis; and (4) levator ani muscles. Collectively, this support provides a firm backboard against which the urethra is supported during increases in intra-abdominal pressure thereby maintaining continence. The proximal two-thirds of the urethra and bladder neck is fused to the anterior vaginal wall, relying greatly on this attachment for support.

Urethral Sphincteric Dysfunction theory

Using a rat model, Kamo and colleagues demonstrated active a closure mechanism in the mid urethra. The investigator used microtip transducer catheters in the proximal and mid urethra to evaluate the urethral closure mechanism under stress conditions induced by sneezing. They noted that, during sneezing, pressure readings increased in the proximal and mid urethra but not in the distal urethra. The response in the proximal urethra was almost negligible when the bladder response was subtracted, suggesting that the proximal urethra closed by passive transmission of increased abdominal pressure. Conversely, the mid-urethral response was still observed after subtracting bladder response, suggesting that the mid urethra closed by an active contraction mechanism in addition to the passive mechanism of the proximal urethra. Moreover, in the mid urethra, the active urethral closure pressure was not related to the magnitude of bladder response, and the urethral response began before the bladder response.

The motor neurons of the external urethral sphincter are located in the ventral horn of the lumbosacral spinal cord in Onuf's nucleus. Stimulation of these neurons evokes contractions of the external urethral sphincter. The external urethral sphincter reflexes are enhanced by serotonin agonists and depressed by serotonin antagonists, suggesting that the descending serotonergic

pathways are responsible for the spinal cord circuitry controlling the closure mechanism of the external urethral sphincter.

NON-SURGICAL TREATMENT FOR STRESS URINARY INCONTINENCE

A. Pelvic Floor Muscle Therapy

This typically involves some method of biofeedback whether it is with e-stimulation or with weighted cones. It needs significant motivation on part of the patient and the results are not instantaneous. With the e-stimulation version, a vaginal probe is used for stimulation of the pelvic floor muscles whereas the rectal probe is used to assess the spontaneous contractions of the pelvic floor. This therapy is done on a weekly basis for about 4-6 weeks and was to sessions been done every couple of months. Approximately half of women with stress predominant urinary incontinence are satisfied one year after starting pelvic floor muscle training.

B. Incontinence Pessaries

Incontinence pessaries are used for patient with stress incontinence mainly as a temporary basis. They could be used in women who are pregnant or desirous of pregnancy. It essentially has a knob that sits under the urethra and causes some degree of urethral compression thereby increasing the urethral resistance.

Sometimes, patients may use a tampon in the vagina however this acts as an absorbent rather than provide a true urethral compression. Urethral plugs have also been used but these should be used temporarily when a patient has just a short bout of incontinence. One randomized trial demonstrated similar satisfaction with stress incontinence symptoms one-year after pessary and behavioral-physical therapy (35) .There was no benefit to combined therapy with pessary and behavioral-physical therapy.

C. Behavioral Modification

Timed voiding is an integral component for the management of urinary stress incontinence. If a woman is going to the bathroom very infrequently, then going to the bathroom every 2-3 hours would help decrease the bladder volume and therefore urinary incontinence. Patient could also be encouraged to empty the bladder prior to engaging in any strenuous activities.

Women should also be informed about the amount of fluid intake and use of caffeinated beverages as these would increase the amount of urine production and bladder volumes. Obesity is an independent risk factor for the development of incontinence, with obese women having a 4.2-fold greater risk of stress urinary incontinence than those with a normal body mass index. Several trials demonstrate that moderate weight loss can improve stress urinary incontinence symptoms in overweight and obese women suggesting that even moderate weight loss can improve stress urinary incontinence.

D. Urethral Bulking Agents

Bulking agents were popularized by the transurethral injection of collagen. This could be done transurethrally or periurethrally. It is mainly indicated in patients who have a fixed urethra without mobility. These patients are unlikely to be benefited by a suburethral sling procedures as the sling would have to be obstructive. Transurethral bulking procedures could also be complimentary to a sling procedure when the patient has noticed improvement but not complete cure. There are different types of agent used such as Macroplastique, Durasphere. Collagen is no longer available.

SURGICAL TREATMENT FOR STRESS URINARY INCONTINENCE

Anterior colporrhaphy

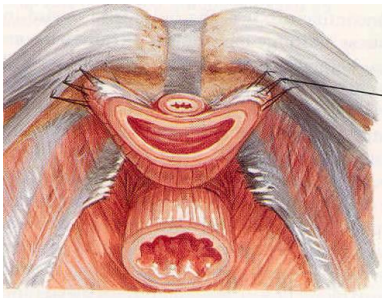
A meta-analysis of eight randomized trials comparing anterior colporrhaphy to other open retropubic techniques demonstrated a higher subjective failure rate for anterior colporrhaphy than for open Burch colposuspension in both the short term (29% versus 14% within 12 months; RR 1.89, 95% CI 1.39–2.59) and long term (41% versus 17% after 12 months; RR 2.50, 95% CI 1.92–3.26). (36)

Needle suspension surgery : Raz and Stamey procedures

A meta-analysis of 10 trials comparing needle suspension techniques to open Burch colposuspension demonstrated a higher failure rate in the needle suspension group (34% versus 23%; RR 0, 95% CI 1.5–2.7). (36)

BURCH COLPOSUSPENSION

The Burch procedure involves attaching the periurethral fascia to the iliopectineal ligament with multiple sutures to stabilize the urethra. The stitches are placed in the space of Retzius and incorporate the fascia overlying the anterior vaginal wall on either side of the bladder neck Traditionally 2 sutures are placed on each side of the bladder neck and attached to the ilio-pectineal (Cooper's) ligament. A suture bridge is maintained in order to prevent excessive overcorrection.



Alcalay et al followed 366 women who underwent colposuspension between 1974 and 1983 and invited them to attend the urogynaecology unit for a 10 to 20 year follow up in January 1994. 109 subjects participated in this study. Objective cure was defined as inability to demonstrate

stress incontinence during clinical examination and provocative urodynamics. They observed that cure rate of stress incontinence is time dependent and therefore survival analysis is an appropriate method to evaluate long term results. Alcalay et al. (37) found that the cure of incontinence following Burch colposuspension was time-dependent, with a decline for 10–12 years when a plateau was reached. at 69%. The most frequent complication of colposuspension in this series was de novo detrusor instability (14· 7 %).

Kjølhede (38) did a follow up of 190 women who underwent open Burch colposuspension and demonstrated significant urinary incontinence in 56% of patients at 14 years, while only 19% of women remained completely dry.

The cure rate of the Burch colposuspension seemed to decline over time. Burch colposuspension is also associated with significant morbidity; recurrent UTI in 4.6%; de novo detrusor instability in 14.7% of patients; long term voiding difficulty in 22% of patients; high rates of pelvic organ prolapse resulted from the Burch (37% in this study).

A Cochrane review done by Lapitan et al of open retropubic colposuspensions, which included 53 studies (*n* = 5,244), reported an overall success rate of 68.9–88.0%.(39)

Incontinence has also been found to be less common after the open Burch procedure (RR 0.38, 95% CI 0.18– 0.76) than after the MMK procedure between 1-year and 5-year follow-up (RR 0.38, 95% CI 0.18–0.76). This meta-analysis also reviewed 12 trials (*n* = 1,260) comparing open Burch procedure to laparoscopic Burch procedure and found no significant difference in patient-reported incontinence between 1-year and 5-year follow-up (RR 0.97, 95% CI 0.75–1.03).(39)

The long-term success of open Burch colposuspension was demonstrated by Sivaslioglu *et al.*(40) in 262 patients with an 84% success rate at 7 years. However, in the longer term success rates decline. Follow-up of 190 women who underwent open Burch colposuspension demonstrated significant urinary incontinence in 56% of patients at 14 years, while only 19% of women remained completely dry.(38)

Overall, the Burch colposuspension has been documented as a safe and effective surgical option for SUI and can be considered for women undergoing an open abdominal procedure for concomitant surgery (for example, pelvic organ prolapse surgery).

Pubovaginal slings

Pubovaginal sling procedures for SUI were introduced at the beginning of the 20th century and remain a feasible option for the management of SUI. (41)

The pubovaginal sling insertion procedure involves abdominal and vaginal incisions with placement of a fascial sling at the proximal urethra. The ends of the sling are passed through the tunnels into the retropubic space and are fixed to the anterior rectus fascia providing support to the urethra during increased intra-abdominal pressure. Alternatively, a suspended sling-on-a-

string method can be used to reduce the invasiveness of the procedure and to shorten the length of sling material required.

Both synthetic (for example, polypropylene) and biologic (autograft [rectus fascia, fascia lata, vaginal skin], allograft [fascia, dermis, dura mater], or xenograft [porcine or bovine]) materials have been used to make pubovaginal slings. In their update on the surgical treatment of SUI from the 4th International Consultation on Urinary Incontinence, Smith *et al.* summarized data from 15 randomized controlled trials (RCTs) reported from 1978 to 2008. Autologous rectus fascia was found to be the most widely evaluated material. However, there was no high-level evidence demonstrating a difference in success rates between biological and synthetic slings. Adverse events were more commonly reported by patients who underwent synthetic sling insertion. (42)

Fascial sling versus Burch randomized clinical study- Stress Incontinence Surgical Treatment Efficacy Trial (SISTr)

The largest trial to date comparing autologous rectus fascia pubovaginal slings to Burch colposuspension was reported by Albo *et al.* in 2007 (2). In their multicenter RCT of 655 women followed for 24 months, success (defined as no self-reported symptoms of SUI, a negative stress test and no retreatment for SUI) was higher in the pubovaginal sling group than the Burch colposuspension group (66% versus 49%; P <0.001). However, pubovaginal slings were associated with an increased risk of UTI (48% versus 32%; P <0.001), voiding dysfunction (14% versus 2%; P <0.001), and postoperative urge incontinence requiring treatment (27% versus 20%; P = 0.04). Brubaker et al from the same group (3) published the results at 5 years in 482 patients (73.6% of the initial cohort), the e-SISTr study (extended Stress Incontinence Surgical Treatment Efficacy Trial) and found that continence rates had decreased substantially in both groups. Overall continence rates were higher in the pubovaginal sling group (30.8%, 95% CI 24.7–36.9) than in the Burch colposuspension group (24.1%, 95% CI 18.5–29.7; P = 0.002). Patient satisfaction decreased from 2 years to 5 years in both groups (from 87% to 83% in the sling group and from 79% to 73% in the Burch colposuspension group) but remained statistically significantly higher for patients who underwent pubovaginal sling insertion (83% versus 73%; P = 0.03). Adverse events were similar in both groups at 24 months (10% in the Burch colposuspension group and 13% in the pubovaginal sling group; P = 0.2) and at 5 years (10% in the Burch colposuspension group and 9% in the pubovaginal sling group).

Long-term data support the use of autologous pubovaginal sling surgery in women with SUI, especially those who have failed other procedures, have had urethral mesh complications (such as vaginal or urethral erosion), or who require a concomitant urethral reconstructive procedure, such as repair of urethral fistula, diverticulum, or destroyed urethra.

The origin of the TVT sling

The midurethral slings were placed via a retropubic approach based on the 'integral theory' of SUI proposed by Ulmsten and Petros.(43)

They postulated that three structures (the pubourethral ligament, the suburethral vaginal hammock, and the pubococcygeus muscles) are closely integrated in a complicated coordination to open and close the bladder neck and urethra. Defects in one of these structures or in their interaction will result in incontinence or voiding dysfunction. Weakness of the pubourethral ligaments results in the inability to adequately occlude the urethra, which contributes to SUI. Based on these assumptions, Ulmsten and Petros designed a minimally invasive surgical procedure; the retropubic approach was devised to reconstitute the pubourethral ligament and the suburethral vaginal supports.

Ulmsten using the Prolene mesh that was 1 centimeter wide and 40 centimeters long published the results of his clinical trial in 1996, included 75 patients with 2 year follow-up and had 92% of patients cured or significantly improved. There were no tape rejection or defective healing, and no intra-operative or post-operative complications. In the mid-1990s, Ethicon met with Dr. Ulmsten and began working with him to create the retropubic TVT sling.

The Prolene mesh Ulmsten used in his first studies was the same mesh that Ethicon used for all of its TVT products, with the exception that a blue dye was added and it was offered in 2006 with a laser or mechanical cut. I have used both and reviewed literature of both and the results are identical and there has been no clinical significance to the laser versus mechanical cut mesh in my practice or the literature.

Ethicon contracted with Dr. Ulmsten and Medscand in 1997 to begin the development and sell of TVT in Europe. I have reviewed the contracts and from a medical point of view there is no concern. By 1998, a multi-center trial with six centers was published with 91% of patient's cured and 7% significantly improved. The results were excellent. Ethicon begin selling TVT in Europe in 1997. With the excellent results from the published studies and reports in Europe the product was launched in 1998 in the United States.

By 2001, there was 5 year data on the TVT showing excellence results. In 2002, studies of up to 3 years showed that TVT did not affect sexual function and there were no women who had dyspareunia as a result of the TVT. In fact, women could expect to have their sexual experience to remain the same or be enhanced with the TVT (44). By May of 2003, Dr. Karram, reported on 350 patients with 4 years follow-up. Erosions and nerve injures were less than 1%. It was determined again that the TVT was safe and effective. The studies continued to show that the TVT was safe and effective. Long term data on TVT now exist all the way up to 17 years that show excellent results without any significant deterioration in success.

Tension-free vaginal tape versus colposuspension for primary urodynamic stress incontinence: 5-year follow up (45)

Ward and Hilton reported the 5-year outcomes of their original RCT, at which time 72 patients in the midurethral sling group and 49 of those in the Burch colposuspension group completed objective and subjective testing. Negative pad tests were reported by 81% of the patients with a midurethral sling compared to 90% of those in the colposuspension group (P = 0.21). 91% of patients with a midurethral sling and 90% of the Burch group were satisfied with the results of the repairs, as reported using the Bristol Female Lower Tract Symptoms questionnaire. Pelvic organ prolapse was more common in the Burch group than the midurethral sling group (42% versus 23% [P = 0.026] for vault prolapse or enterocele; 49% versus 32% [P = 0.023] for rectocele), and mesh erosion occurred in four women in the midurethral sling group (three vaginal; one bladder). Reoperation rates for SUI were similar (3.4% for colposuspension and 2.3% for TVT™; P = 0.74). Overall, similar success was reported for both procedures at 5 years.

Based on a systematic literature search performed in January 2007, Novara et al (46, 47) reported two systematic reviews and meta-analyses of randomized controlled trials (RCTs) evaluating the efficacy and complication rates of TVT compared with Burch colposuspension, pubovaginal slings, and other midurethral tapes. On the whole, the data from the two meta-analyses suggested that TVT was significantly more effective than colposuspension and was followed by similar complication rates; the data also showed that TVT was similar in efficacy to pubovaginal slings, which are followed by significantly higher perioperative morbidity. Finally, the two meta-analyses demonstrated that TVT and Transobturator slings (TOT) had similar efficacy, although the risk of bladder perforations, pelvic hematoma, and storage lower urinary tract symptoms (LUTS) was significantly less common in patients treated with TOT

The retropubic sling can be placed via a top-down approach or a bottom-up approach. For the top-down approach, an incision is made in the anterior vaginal wall and the periurethral space is dissected. Trocars are passed through small incisions in the anterior abdominal wall just superior to the pubic bone. The trocar passes retropubically and exits through the dissected periurethral space. The sling (for example, Lynx® [Boston Scientific, USA] or SPARC™ [American Medical Systems, USA]) is then attached to the trocar and the trocars are removed, placing the sling under the midurethra in a tension-free manner. For the bottom-up approach, the trocars are passed vaginally through the dissected periurethral space. They travel retropubically and exit through the anterior abdominal wall superior to the pubic bone. The sling (such as the TVT™ or the Advantage® [Boston Scientific, USA]) is then attached to the trocar and the trocar is removed.

Rehman *et al.* (48) conducted a meta-analysis to determine the outcomes of traditional pubovaginal slings versus other surgical options for SUI, including synthetic midurethral slings. In eight trials including 693 patients they found an equal rate of short-term success (at 12 months) between pubovaginal slings and midurethral slings (RR 0.97, 95% CI 0.78–1.20).

Ogah et al (49) performed a meta-analysis of 62 trials involving 7,101 patients and evaluated the short-term clinical effects of minimally invasive synthetic midurethral sling procedures for the treatment of both urodynamic SUI and clinically symptomatic SUI. Eight RCTs (599 patients) compared synthetic midurethral slings with pubovaginal slings, and the overall subjective cure rate within 12 months was similar between the two (73% vs 71%, RR 1.03, 95% CI 0.94–1.13). However, the midurethral slings are associated with shorter operative times, quicker recovery, and fewer postoperative complications . Rates of new onset urgency and urgency incontinence are lower after midurethral sling compared to bladder neck slings.

In 2010 Novara *et al.* (50) added 14 new trials to their 2007 systematic review and meta-analysis that evaluated the efficacy, complication rate and reoperation rate of Burch colposuspension, pubovaginal slings and synthetic midurethral slings. Only two trials reported follow-up >60 months. Midurethral slings were found to have a higher objective cure rate than Burch colposuspension (OR 0.38, 95% CI 0.25–0.57; P <0.0001) but a similar subjective cure rate (OR 0.79, 95% CI 0.52–1.21; P = 0.27).

One meta-analysis (49) has compared the bottom-up TVT™ and the top-down SPARC™ , and found that women who underwent the bottom-up approach had significantly fewer bladder perforations (4.7% versus 8.5%; RR 0.55, 95% CI 0.31–0.98), fewer vaginal tape erosions (0.7% versus 3.5%; RR 0.27, 95% CI 0.08–0.95), and reported significantly higher subjective (85% versus 77%; RR 1.1, 95% CI 1.01–1.2) and objective cure rates (92% versus 87%; RR 1.06, 95% CI 1.01–1.11). There was no difference in QOL outcomes.

LONG TERM STUDIES ON TVT-- UPTO 17 YEARS FOLLOW UP!

Seventeen years' follow-up of the tension-free vaginal tape procedure for female stress urinary incontinence: C. G. Nilsson (51)

The study population consisted initially of 90 consecutive women diagnosed with primary stress urinary incontinence. Of the women who potentially could have been assessed, 58 out of 74 (78.4 %) were evaluated in some way. Forty-six women were evaluated according to the protocol at the clinics. The mean follow-up was 201 months (16 years and 9 months) with a range between 185 and 213 months. Objective cure, defined as a negative stress test, was seen in 42 out of 46 women (91.3 %). The PGII revealed that 48 out of the 55 women (87.2 %) regarded themselves cured or significantly better than before surgery, 5 out of 55 (9.1 %) experiencing no change and 2 out of 55 (3.6 %) worse than before surgery.

To the question, do you experience leakage during straining, 42 out of 53 (79.2 %) answered no and 50 out of 51 (98 %) would recommend the TVT procedure to a friend. The actual percentage of those lost to follow-up was thus 22 %, which is fairly low for a period of almost two decades. The objective cure rate, assessed by the stress test, was 91 % and showed no decline between 5 and 17 years' follow-up. The corresponding subjective perception of either cure or improvement was over 87 %, with a slight decline during the last 6 years, probably mostly due to urgency incontinence.

Nielsen et al make very keen observations based upon this long term 17 year follow up study:

There seems to be no shrinkage of the TVT mesh over time, as suggested by postvoid residual volumes within normal ranges, except for 2 patients with concomitant diseases (Parkinson's, grade III cystocele).

The mesh complications seen in association with urogenital prolapse surgery that have alerted the FDA might not be caused by the mesh material itself. As long as a type I material is used the complications could be the result of improper training of the surgeon, resulting in an inappropriate surgical technique or choosing the wrong indication or wrong patient for the graft procedure.

The present report suggests that using a type I, macroporous, monofilament, lightweight, and soft polypropylene mesh, the risk of mesh complications even 17 years after implantation under the vaginal mucosa is negligible provided the surgery is performed by a trained and experienced surgeon.

Olsson et al (52) conducted a retrospective long term follow up of 11.5 years following the retropubic TVT procedure. 124 women undergoing TVT have been followed-up 11.5 years post-operatively. In the study group of 104 women, they found an objective cure rate of 84 % according to a negative stress test, while the subjective cure in the whole group was 77 %.

The new gold standard

Chugtai (53**)** reviewed a total of 6355 nonpediatric urologists applied for certification or recertification between 2003 and 2012. Two-thirds (4185) reported performing any procedures for female incontinence. Procedures sharply increased from 4632 in 2003 to 7548 in 2004, then remained relatively stable between 2005 and 2012 (range, 8014-10,238 cases). Traditional procedures decreased from 17% of female incontinence procedures in 2003 to 5% in 2004 to <1% since 2010 (P <.0005). Midurethral sling procedures have risen sharply from 3210 procedures in 2003 to 7200 in 2012 (P <.0005). Endoscopic injection treatments have remained stable. Slings comprised of 69% of the female incontinence procedures for SUI in 2003; whereas in 2012, slings increased to 86%.This study which evaluated data from the ABU, showed that midurethral slings and urethral bulking agents are the only procedures performed currently for female SUI, with 5 times as many midurethral slings performed as urethral bulking agents.

A study from 2015 evaluating the IUGA members' practice patterns showed that the preferred method of treatment for SUI is the midurethral sling, regardless of prior treatments, concomitant surgeries, or examination findings (54). "Synthetic midurethral slings are predominant in the current treatment of SUI." "The treatment of stress incontinence has shifted in recent years, with the initial survey showing a predilection for the Burch colposuspension as a primary and secondary surgical treatment for normal pressure urethral SUI (44 and 41%), while the current survey revealed that 2% of respondents were performing the Burch procedure as a primary SUI

treatment and 11% of respondents were using it as a secondary treatment." TVT is the preferred treatment for patients with ISD.

TRANSOBTURATOR SLINGS

The transobturator approach was introduced in 2001by deLorme (55) with the aim of decreasing the risks of perioperative bladder, bowel, and vascular complications reported rarely with the retropubic approach. Based on the 'hammock theory' of female SUI proposed by Delancey(33) in 1994, the mesh is placed under the urethra through the obturator membrane and obturator internus muscle in the horizontal plane. The hammock theory states that both urethral support and constriction are necessary for continence and that multiple tissue layers (including the anterior vaginal wall, endopelvic fascia and pelvic floor muscles) are responsible for this support and constriction. Based on this theory, the mesh provides support for the urethra at times of increased intra-abdominal pressure, thus preventing urinary leakage.

Transobturator mesh can be placed via an outside-in approach (Monarc™ [American Medical Systems, USA], ObTryx® [Boston Scientific, USA], Aris [Coloplast, USA]) or an inside-out approach (TVT-O™ [Ethicon, USA], Abbrevo™ [Ethicon, USA]).

First, an incision is made in the anterior vaginal wall and the periurethral space is dissected. For the outside-in approach, the trocar is passed into the inner thigh (a small puncture made inferior to adductor longus tendon at the level of the clitoral hood) through the obturator membrane and exits through the periurethral dissection. The sling is attached and the trocar removed, passing the sling into position. For the inside-out approach, the sling is attached to the trocar, which is passed from the incision in the vaginal wall, through the obturator membrane and out through the inner thigh. The trocar is then removed leaving the sling *in situ.*

The safety and efficacy of the inside-out TVT-O™ was investigated by Waltregny *et al.*, (56) whose prospective, observational trial found a subjective and objective cure rate of 91% for 253 women at 12 months' follow-up. Postoperative voiding symptoms were reported in <10% of patients. No bladder or urethral perforations occurred during the procedures, and no vaginal or urethral mesh erosions were noted after surgery. QOL, assessed using the Ditrovie self-questionnaire, was significantly better after surgery than at baseline (P <0.0001). Follow-up at 3 years revealed similar results. (57)

The inside-out and outside-in approaches to the transobturator midurethral sling have been compared in several meta-analyses. Novara *et al. (50)* reported an equal rate of objective success between the two approaches at 4 months in three trials comprising 280 patients who underwent transobturator mesh sling insertion (OR 1.96, 95% CI 0.84–4.53; P = 0.12). Latthe *et al.(58)* also found an equal rate of both subjective (OR 1.37, 95% CI 0.93–2.00; P >0.05) and objective success rates (OR 1.06, 95% CI 0.65–1.73; P >0.05). Bladder injury and voiding difficulties were less frequent with the inside-out technique than the outside-in technique (OR 0.17, 95% CI 0.005–0.05 and OR 0.49, 95% CI 0.24–1.04, respectively).

Moreover, multiple studies confirm that TVT-O is safe and effective in the long term. These studies include: Tommaselli GA, *Tension-free vaginal tape-obturator and tension-free vaginal tape-Secur for the treatment of stress urinary incontinence: a 5-year follow-up randomized study*. Eur J Obstet Gynecol Reprod Biol. 2015 Feb; 185:151-5; Tommaselli GA, *Medium-term and long-term outcomes following placement of midurethral slings for stress urinary incontinence: a systematic review and metaanalysis*. Int Urogynecol J. 2015 May 20; Athanasiou S, *Seven years of objective and subjective outcomes of transobturator (TVT-O) vaginal tape: why do tapes fail?* Int Urogynecol J. 2014 Feb; 25(2):219-25. Laurikainen E, *Five-year results of a randomized trial comparing retropubic and transobturator midurethral slings for stress incontinence*. Eur Urol. 2014 Jun;65(6):1109-14; Serati M, *TVT-O for the treatment of pure urodynamic stress incontinence: efficacy, adverse effects, and prognostic factors at 5-year follow-up*. Eur Urol. 2013 May; 63(5):872-8; Cheng D, *Tension-free vaginal tape-obturator in the treatment of stress urinary incontinence: a prospective study with five-year follow-up*. Eur J Obstet Gynecol Reprod Biol. 2012 Apr; 161(2):228-31; Liapis A, *Efficacy of inside-out transobturator vaginal tape (TVTO) at 4 years follow up*. Eur J Obstet Gynecol Reprod Biol. 2010 Feb; 148(2):199-201.

TVT OR THE TVT-O PROCEDURE

Novara *et al.* (50) found the retropubic approach was associated with a significantly higher rate of objective success than the transobturator technique (OR 0.8, 95% CI 0.65–0.99; $P = 0.04$). Subjective success rates were equivalent. The obturator approach resulted in fewer bladder and vaginal perforations (OR 2.5, 95% CI 1.75–3.57; $P < 0.0001$) and fewer patients with storage lower urinary tract symptoms (OR 1.35, 95% CI 1.05–1.72; $P = 0.02$).

Ogah *et al.* (49) compared retropubic and obturator slings in a meta-analysis that included 24 trials. Subjective cure rates at 12 months were available for a total of 1,381 patients. No statistically significant difference was found between retropubic and transobturator slings, with patients in both groups reporting an 83% success rate (RR 1.00, 95% CI 0.96–1.05). Objective cure rates at 12 months for 2,434 patients were 88% and 84% in the retropubic and transobturator groups, respectively (RR 0.96, 95% CI 0.93–0.99).

Richter *et al.* (4) reported the outcomes of 597 women randomized to undergo either retropubic ($n = 298$) or transobturator ($n = 299$) midurethral sling insertion. Self-reported symptoms, urinary stress tests, pad tests and retreatment rates were assessed. Objective success rates (defined as a negative provocative stress test, a negative 24 h pad test and no retreatment for SUI) at 12 months were 80.8% in the retropubic group and 77.7% in the obturator group (3% difference, 95% CI 3.6–9.6). Statistical analysis demonstrated equivalence for both procedures in objective measures; however, retropubic slings performed slightly better subjectively (62.2% versus 55.8%; 6.4% difference, 95% CI 1.6–14.3). Intraoperative blood loss was greater in the retropubic group than the transobturator group (50 cc versus 25 cc; $P < 0.001$), as was the operative time (30 min versus 25 min: $P < 0.001$). Although these values were statistically significant, they are unlikely to be clinically significant. The rate of serious adverse events was 13.8% in the retropubic group and 6.4% in the transobturator group ($P < 0.03$), with higher rates of UTI ($P = 0.04$), bladder perforation (5% versus 0%) and voiding dysfunction requiring

surgical intervention (2.7% versus 0%; *P* = 0.004) reported by those who underwent retropubic sling insertion. Neurologic complications (new paresthesias or motor deficit at 6 weeks) were more common in the transobturator group (9.4% versus 4.0%; *P* = 0.01) as were vaginal perforations (4.3% versus 2.0%). No significant differences in *de novo* urge incontinence, patient satisfaction or QOL were reported between groups. Mesh complications (3.4%) were uncommon (16 exposures and 2 erosions) in the first 2-years. There were only 7 new mesh erosions (3 TVT™, and 4 transobturator slings) between year 2 and 5.

Overall, these data suggest that the retropubic approach offers a slight advantage over the transobturator approach in terms of objective cure rates. Each technique is associated with a different adverse effect profile; with the retropubic approach causing a higher rate of perioperative complications.

COMPLICATIONS OF THE TVT AND TVT-O PROCEDURES ARE MINIMAL

A 2015 Cochrane Review of the peer reviewed literature concluded that "midurethral sling operations are the most extensively researched surgical treatment for stress incontinence in women, have a good safety profile…. and are highly effective in the short and medium term… accruing evidence demonstrates their effectiveness in the long term." (59). The authors also conclude that midurethral slings have a "positive impact on improving quality of life of women with stress incontinence."

Ford (59) reported the following complication rates from registries for the retropubic midurethral sling: bladder perforation 2.7 – 3.9%, reoperation rates relating to tape insertion or postoperative voiding dysfunction 1.6% - 2.4%, urinary retention rate was 1.6%, pelvic hematoma 0.7% - 1.9%, infection rate was 0.7%, vaginal tape erosion/extrusion rate was 1.5%, groin pain occurred in 0.4% of women. Similar rates were reported for transobturator slings: bladder perforation 0.4%, reoperation rates relating to tape insertion 0.8% - 2.2%, urinary retention 0.5%, pelvic hematoma 0.5%, infection rate 0.6%, vaginal tape erosion/extrusion rate was 0.4%, and groin pain occurred in 1.6% of women.

These rates are consistent with the FDA's analysis of complication rates from the MAUDE database showing around 2% mesh exposure, and the Medicines and Healthcare Products and Regulatory Agency (MHRA) in Europe publishing a low vaginal tape erosion rate between 1.1% to 2.5%. In their 2014 report, the MHRA concluded that there appeared to be no evidence that vaginal mesh implants for SUI are unsafe. Moreover, over 50% of the mesh exposures are managed expectantly as the patients are asymptomatic. Native tissue repairs with permanent or absorbable sutures can also result in suture exposures and erosions, which could require a re-operation or simple office excision of the exposed or eroded suture.

Post-operative chronic pain and dyspareunia are rare complications associated with both the retropubic and transobturator midurethral sling (60).

GROIN PAIN

Persistent pain in the groin or thigh is another troublesome complication of midurethral slings that occurs more commonly with the transobturator approach than retropubic surgery. Laurikainen *et al.*(61) reported that 16% of women randomized to undergo insertion of an inside-out transobturator sling experienced groin pain compared with only 1.5% of those in the TVT arm. Similarly, Wang and colleagues (62) reported pain in 8.2% of patients after TVT-Ocompared with only 2.6% of those who underwent TVT insertion. In meta-analyses, Long *et al.*(62) and Latthe *et al.*(58) confirmed that groin or thigh pain was reported more frequently after transobturator insertion than retropubic procedures.

However, groin or leg pain with TVT-O is usually transient and typically resolves in the post-operative period. The literature has shown that while TVT-O has a higher rate of groin pain than TVT in the immediate post-operative period, the groin pain rarely persists in the long-term. At 7.5 year follow-up, Athanasiou (63) found that no patients reported persistent groin pain at the longterm follow-up. Similarly, Serati (64) and colleagues found that 9.9% of patients complained of groin pain 24 hours after the TVT-O procedure, while 3.1% complained of groin pain at six month follow-up, 1% at one year follow-up, and at 5 years, no cases of groin pain remained.

Recent systematic reviews by Ford (59) and Tommaselli(65) evaluating the safety of retropubic and transobutrator midurethral slings concluded that 'midurethral sling operations have been the most extensively researched surgical treatment for stress urinary incontinence in women and have a good safety profile. Irrespective of the routes traversed, they are highly effective in the short and medium term and accruing evidence demonstrates their effectiveness in the long term." When comparing transobutator and retropubic approaches, the authors of the Cochrane Review found that there were no statistically significant differences in rates of overall perioperative complications between the procedures. Overall, vaginal mesh exposures were not different for retropubic or transobturator midurethral slings (approximately 2%).

Rates of postoperative pain were low with both transobturator and retropubic midurethral slings (4.5%), and when pain was reported the 'occurrences were short lasting, with most resolving in the first 6-months'. Tommaselli found no differences in postoperative pain (OR 0.78) nor persistent voiding dysfunction (OR 1.23) between retropubic midurethral slings or transobturator midurethral slings. The authors concluded that the similar efficacy of retropubic and transobturator midurethral slings is "backed by a high safety profile, and by a limited number of complications which were seldom severe."

In summary, for women considering a retropubic or transobturator MUS, Schimpf et al (60) recommend either the TVT or the Transobturator TVT-O intervention as the objective and subjective cure are similar; the decision should be based on surgeon expertise accounting for adverse events.

Post-operative chronic pain and dyspareunia are rare complications associated with both the retropubic and transobturator midurethral sling (60). In a randomized trial of 565 women undergoing TVT or transobturator sling, only 2% of those undergoing TVT reported any pain beyond 6-weeks after surgery. Pelvic pain and dyspareunia are common conditions among the general population, even for women who haven't undergone pelvic surgery, and have also been reported in the medical literature for traditional procedures (66). TVT has been shown to improve sexual function. (67)

SOCIETY STATEMENTS ARE IN FAVOR OF THE TVT MESH

The American Urogynecologic Society (AUGS), American Urological Association (AUA) and National Institute of Health and Care Excellence (NICE) have all come out with position statements on SUI treatments. These organizations and others have concluded that the TVT and TVT-O have been extensively studied and are safe and effective. Complications are low, morbidity is minimal, and the TVT and the TVT-O are as or more efficacious than other procedures. Further, NICE reported five devices for the treatment of SUI which had high quality efficacy and safety data and two of the five were TVT and TVT-O. NICE also stated that devices should use type 1 macroporous polypropylene tape, for which the TVT is made.

The AUA Position Statement (68) approved in 2011 and revised in 2013 noted the following about the safety profile and utility of synthetic midurethral slings such as TVT:

- Suburethral synthetic polypropylene mesh sling placement is the most common surgery currently performed for SUI. Extensive data exist to support the use of synthetic polypropylene mesh suburethral slings for the treatment of female SUI, with minimal morbidity compared with alternative surgeries. Advantages include shorter operative time/anesthetic need, reduced surgical pain, reduced hospitalization, and reduced voiding dysfunction.

- Mesh-related complications can occur following polypropylene sling placement, but the rate of these complications is acceptably low. Furthermore, it is important to recognize that many sling-related complications are not unique to mesh surgeries and are known to occur with non-mesh sling procedures as well. It is the AUA's opinion that any restriction of the use of synthetic polypropylene mesh suburethral slings would be a disservice to women who choose surgical correction of SUI.

- Additionally, both the Society of Urodynamics, Female Pelvic Medicine and Urogenital Reconstruction (SUFU) and the AUA support the use of multi-incision monofilament midurethral slings for the treatment of SUI in properly selected patients who are appropriately counseled regarding this surgical procedure by surgeons who are trained in the placement of such devices, as well as the recognition and management of potential complications associated with their use.

- Multiple case series and randomized controlled trials attest to the efficacy of synthetic polypropylene mesh slings at 5-10 years. This efficacy is equivalent or superior to other surgical techniques. There is no significant increase in adverse events observed over this period of

follow-up. Based on these data, the AUA Guideline for the Surgical Management of Stress Urinary Incontinence (2009) concluded that synthetic slings are an appropriate treatment choice for women with stress incontinence, with similar efficacy but less morbidity than conventional nonmesh sling techniques.

AUGS (with over 1,700 members) and SUFU (with over 500 members) adopted a joint position statement in 2014 highlighting the following about the safety and efficacy of midurethral slings:

- The polypropylene mesh midurethral sling is the recognized worldwide standard of care for the surgical treatment of stress urinary incontinence. The procedure is safe, effective, and has improved the quality of life for millions of women.

- Polypropylene material is safe and effective as a surgical implant. Polypropylene material has been used in most surgical specialties (including general surgery, cardiovascular surgery, transplant surgery, ophthalmology, otolaryngology, gynecology, and urology) for over five decades, in millions of patients in the US and the world (personal communication with manufacturers of polypropylene suture and mesh). As an isolated thread, polypropylene is a widely used and durable suture material employed in a broad range of sizes and applications. As a knitted material, polypropylene mesh is the consensus graft material for augmenting hernia repairs in a number of areas in the human body and has significantly and favorably impacted the field of hernia surgery. As a knitted implant for the surgical treatment of SUI, macroporous, monofilament, light weight polypropylene has demonstrated long term durability, safety, and efficacy up to 17 years. [51].

- The monofilament polypropylene mesh MUS is the most extensively studied anti-incontinence procedure in history. A broad evidence base including high quality scientific papers in medical journals in the US and the world supports the use of the MUS as a treatment for SUI. There are greater than 2000 publications in the scientific literature describing the MUS in the treatment of SUI. These studies include the highest level of scientific evidence in the peer reviewed scientific literature. The MUS has been studied in virtually all types of patients, with and without comorbidities, and all types of SUI. Multiple randomized, controlled trials comparing types of MUS procedures, as well as comparing the MUS to other established non-mesh SUI procedures, have consistently demonstrated its clinical effectiveness and patient satisfaction. Among historical SUI procedures, the MUS has been studied as long in follow-up after implantation as any other procedure and has demonstrated superior safety and efficacy. No other surgical treatment for SUI before or since has been subject to such extensive investigation.

- Polypropylene mesh midurethral slings are the standard of care for the surgical treatment of SUI and represent a great advance in the treatment of this condition for our patients. Over 3 million MUS have been placed worldwide and a recent survey indicates that these procedures are used by > 99% of AUGS members.

IUGA approved a similar position statement in 2014 describing the safety and efficacy of midurethral slings:

- Stress urinary incontinence is a common, burdensome and costly condition for women with a negative impact on quality of life.

- There is robust evidence to support the use of MUS from over 2,000 publications making this treatment the most extensively reviewed and evaluated procedure for female stress urinary incontinence now in use.
- As a result, IUGA supports the use of monofilament polypropylene mid-urethral slings for the surgical treatment of female stress urinary incontinence.

The European Association of Urology's 2012 Guidelines and Recommendations for treating urinary incontinence:

- Offer midurethral sling to women with uncomplicated stress urinary incontinence as the initial surgical intervention whenever available.
- Offer colposuspension (open or laparoscopic) or autologous fascial sling to women with stress urinary incontinence if midurethral sling cannot be considered.
- Warn women undergoing autologous fascial sling that there is a high risk of voiding difficulty and the need to perform clean intermittent selfcatheterization; ensure they are willing and able to do so.

The National Institute of Health Care and Excellence (NICE) set forth criteria for treating stress urinary incontinence in the 2013 Guideline, including:

- If conservative management for SUI has failed, offer: synthetic mid-urethral tape; open colposuspension; autologous rectus fascial sling.
- Section 1.10.3: Synthetic tapes: When offering a synthetic mid-urethral tape procedure, surgeons should: use procedures and devices for which there is currently high quality evidence of safety and efficacy : The guideline only recommends the use of tapes with prove efficacy based on robust RCT evidence… TVT for retropubic approach; TVT-O for an "inside-out" transobturator approach….

AUGS-SUFU FAQs by Providers on Mid-urethral Slings for SUI
2014 Mar 12

Does the evidence indicate that mid-urethral slings are effective for the treatment of SUI?
Among historical SUI procedures, the MUS has been studied as long in follow-up after implantation as any other procedure and has demonstrated superior safety and efficacy. This includes a recent 17 year follow-up study. No other surgical treatment for SUI before or since has been subject to such extensive investigation.

Does the evidence indicate that mid-urethral slings are safe in the treatment of SUI?
The MUS is the most studied anti-incontinence procedure in medical history. Furthermore, it is likely that more individuals have undergone this surgical procedure for the treatment of SUI than any other.

What is the material used for mid-urethral slings and have studies shown the material to be safe?

Currently available mid-urethral slings are composed of macroporous, knitted, monofilament polypropylene, sometimes known as "Type I" meshes. As a suture material, polypropylene is widely used, durable and employed in a broad range of sizes and applications. Polypropylene material has been used in most surgical specialties (including general surgery, cardiovascular surgery, transplant surgery, ophthalmology, otolaryngology, gynecology, and urology) for over five decades, in millions of patients in the US and the world.

Does the MUS mesh made of polypropylene degrade over time?

Polypropylene is a stable and well-accepted biomaterial with a history of over five decades of use in mesh implants. In recent years, concerns regarding implanted polypropylene degradation have been raised as a result of very high-magnification images that show portions of some explanted synthetic meshes with "cracked" surfaces.[8] These surface changes were further hypothesized to lead to adverse clinical outcomes, though this is not supported by the extensive peer-reviewed literature related to polypropylene mesh repairs.

Is there scientific evidence that the mesh used in polypropylene mid-urethral slings causes cancer in humans?

Tumors related to the implantation of surgical grade polypropylene for mid-urethral slings in humans have never been reported. There is no compelling evidence supporting human malignant transformation related to polypropylene despite the millions of individuals implanted with various forms of this material spanning well over a half century world-wide. The possibility that biomaterial prosthetic devices could cause tumors or promote tumor growth has been the focus of extensive research by both clinicians and biomaterial researchers. It is known that tumor formation related to biomaterials in animals is largely dependent on the physical, not the chemical configuration of the implant, with smooth large surface areas (discs and thin sheets) being potentially carcinogenic, and irregular disrupted surfaces (e.g. those that contain pores as in meshes) lacking carcinogenicity.

Has there been an FDA recall of mid-urethral slings or the mesh material?

None of the FDA communications regarding mesh used in pelvic reconstructive surgery were related to a recall nor did they suggest that the material or implantation of mid-urethral slings were dangerous, or should be stopped.

Has the FDA warned against surgical placement of mid-urethral slings?

In 2013, the FDA website stated clearly that: "The safety and effectiveness of multi-incision slings is well-established in clinical trials that followed patients for up to one-year." The FDA

has specifically exempted full-length mid-urethral slings from the need for additional mandated research.

What is a 522 study and does it involve mid-urethral slings?
A 522 study refers to a specific section of the FDA regulatory framework wherein a commercial entity is required to perform additional post-marketing research following its regulatory approval by the FDA. Once 522 studies are mandated, they are subject to FDA oversight.

I agree with all these various professional society statements as they are consistent not just with my clinical experience, but my extensive review of the medical literature.

Mesh in TVT and TVT-O

I am familiar with the size the TVT mesh, its appropriateness in the body and use for SUI, its tissue response. The TVT mesh is a monofilament polypropylene Type 1 macroporous mesh as defined by NICE and Amid classification. This Prolene mesh provides an appropriate strength, elasticity, inflammatory response, resistance to infection, good integration that allows for a successful repair. Per Moalli the TVT mesh is 1379 microns and is therefore a large pore mesh. This pore size provides plenty of room for tissue integration as seen in literature and in my practice. The strength of the mesh is necessary to provide support when the stress is placed on the urethra. In addition, moving to larger pore meshes could provide more elasticity and could likely lead to an increased result of SUI.

I have reviewed the MSDS sheets and any claims that polypropylene mesh causes sarcomas or that mesh degrades are baseless and never seen in clinical practice.

Ultrapro is Not a Safer Alternative Design for TVT or TVT-O:

Some plaintiffs' experts have speculated that the use of a partially absorbable mesh, such as Ultrapro or Vypro would be a safer alternative material than the TVT mesh for treating stress urinary incontinence. They rely on the Okulu (77) study which is not a well-powered study and did not directly compare the hand-made (mechanically cut) Ultrapro pubovaginal sling to TVT or TVT-O. These claims are without reliable scientific support.

Also, the opinion that a lighterweight mesh is a safer alternative design ignores that Ethicon tried unsuccessfully to manufacture a lighterweight mesh. This attempt suffered six failed cadaver labs and the FDA rejected it's clearance application.

TVT polypropelene sling: material and design

P.K.Amid Lichtenstein Hernia Institute, Inc., Los Angeles, California, USA, Received March 17, 1997
Accepted in final form March 25, 1997

Based on their pore size, the most frequently-used materials can be grouped into four types:

Type I: Totally macroporous prostheses, such as Atrium, Marlex, Prolene and Trelex. These prostheses contain pores larger than 75 microns, which is the required pore size for admission of macrophages, fibroblasts (fibroplasia), blood vessels (angiogenesis) and collagen fibers into the pores.

Type II: Totally microporous prostheses, such as expanded PTFE (Gore-Tex), Surgical Membrane. These prostheses contain pores that are less than 10 microns in at least one of their three dimensions.

Type III: Macroporous prosthesis with multifilamentous or microporous components, such as PTPE mesh (Teflon), braided Dacron mesh (Mersilene)

Type IV: Biomaterials with submicronic pore size, such as silastic, Cellgard (polypropylene sheeting), Preclude Pericardial membrane and Preclude Durasubstitute

Surgical infection promoted by implantation of biomaterials, such as sutures and prostheses, is caused by infiltration and proliferation of bacteria into and within the pores and interstices of these synthetic materials. When interstices or pores are less than 10 microns, in each of their three dimensions, bacteria averaging 1 micron cannot be eliminated by macrophages and neutrophilic granulocytes, which are too large to enter a 10 microns three-dimensional pore.

Contrary to Type II and III, Type I prostheses deter housing and growth of bacteria, not only by admitting macrophages, but because they allow rapid fibroplasia and angiogenesis within their sufficiently wide pores, which also prevents infiltration and growth of bacteria .

More importantly, in connection with surgical infection, the totally macroporous protheses (Type I) do not have to be removed; drainage of the infected area, followed by local wound care and antibiotics, is all that is necessary to manage the infection.

TVT slings are type I polypropelene macroporous slings and allow for the free passage of macrophages which form the basis of the foreign body reaction which is protective against infection.

In ***Polypropylene: the Standard of Mesh Materials*** A.I. Gilbert et al. (**Meshes: Benefits and Risks** Schumpelick; SpringerVerlag Berlin Heidelberg 2004) notes the following, with which I agree:

> Polypropylene mesh is produced from polypropylene. Polypropylene (PP) in its monofilament form is derived from the controlled polymerization of propylene. Propylene is derived from propane gas. It is heat-resistant up to 168.3° C. or 335° F, thereby allowing it to be sterilized without compromise. PP possesses high tensile strength and good flexibility leading to its primary medical use as a suture material. It has excellent resistance to infection.
> Medical-grade PP provokes the least foreign-body reaction due to the minimal use of catalysts and additives needed to produce it.
>
> To manufacture PPM, hooked needles are used to interlock the PP filament to form vertical and crosswise rows of loops. The crosswise rows of loops are courses. The lengthwise rows of loops are wales.

Laser cut vs. mechanically cut TVT mesh

The initial slings that were brought out into the market were mechanically cut slings. Most of the clinical trials that have been done in the literature involve mechanically cut slings. It has been studied in over a 1000 studies and found to be clinically effective without any intrinsic defect. There was a change in the way the TVT and TVT-O mesh was cut from mechanical to laser cut slings. Beginning in 2007 both the mechanically cut and the laser cut slings become available—and still are to this day. This was due to the fact that there were a vast number of surgeons who were happy with the mechanical cut sling and did not want to change what was working well.
Review of internal documents from Ethicon regarding the medical interpretation of biomechanical engineering test data shows no difference on the product physical characteristics.

I also reviewed the plaintiff's expert's report quoting the Ethicon emails and further stating that the mechanically cut slings lead to significant fraying, roping, curling and also particle loss. I am also aware of a TVT SECUR study by Neuman (70) where he hypothesized that the sharp edge of the laser cut TVT SECUR sling could possibly increase the risk of erosion by cutting the vaginal epithelium.

However, this theory is not substantiated in the peer-reviewed literature, nor in my vast clinical experience.

As shown by the Ethicon engineers, the fraying of the mechanically cut sling only happens when it is subject to high stress tensions which are never encountered in a normal human body under physiological stress. Moreover, when the long slings (TVT, TVT-O) are placed, they have to be placed in a tension-free manner. If a spacer is placed correctly between the sling and the urethra

and the plastic sheaths are pulled out carefully and not vigorously, there should be no stretching of the sling. Therefore, under normal conditions of sling placement using the tension-free concept, there is no evidence of any probing, curling or fraying of the edges.

Additionally, plaintiffs' experts' suggestion that the TVT and TVT-O laser cut mesh is three times stiffer than mechanically cut mesh, and therefore, is more prone to causing mesh exposures conflicts with these data. As evidenced by the data – not the theories – from the Neuman study, this logic does not carry weight since the laser cut TVT Secur group had a 0% rate of mesh exposure.

The difficulty that some surgeons have encountered while removing the inserter is more to do with the surgical technique than a defect in the product or a problem with the IFU.

My opinion based upon reasonable degree of medical certainty, my experience doing sling procedures, review of the literature and discussion with my colleagues, is that there is no substantiated evidence that a mechanically cut sling causes more fraying in vivo and is worse than a laser cut sling.

THE TVT IFU IS ADEQUATE

I have reviewed the Information of Use (IFU) of TVT and TVT-O and state that it is adequate. The TVT and TVT-O IFU and Professional Education materials adequately warn pelvic floor surgeons of the risks associated with the TVT and TVT-O device.

It is the responsibility of every surgeon to review the IFU for that particular procedural device. The IFU is written for surgeons and not for patients. Case in point: TVT's first IFU states that "This device should be used only by physicians trained in the surgical treatment of Stress Urinary Incontinence."

Based on my experience in doing over 300 TVT procedures, outcome analysis of this procedure by way of clinical trials, review of the medical literature that has been published on the TVT and TVT-O, performance of the cadaver courses and Proctorship at cadaver courses and at live surgery when teaching visiting doctors or residents on performing the TVT and TVT-O procedures, and my interaction with fellow surgeons at these events it is my opinion that the IFUs for TVT and TVT-O and Ethicon's other professional education materials like the TVT Surgeon's Resource Monograph adequately describe the risks that are specific and/or unique to TVT and TVT-O. Additionally, I believe that the surgical risks and complications—and not warnings about plaintiff-alleged design flaws—that plaintiffs' experts say should be included in the TVT and TVT-O IFUs are risks that are generally known to pelvic floor surgeons. These opinions are based on the following:

- Although I am not a regulatory expert, I have reviewed 21 C.F.R. 801.109(c), which permits the omission of risk information if "the article is a device for which directions, hazards, warnings, and other information are commonly known to practitioners licensed by law to use the device." Also, the FDA's "Blue Book Memo" says basically the same thing, stating that information may not be included in a warning label if "the directions, hazards, warnings, and other information are commonly known to practitioners licensed by law to use the device…"
- The body of TVT and TVT-O medical literature that records success and complication rates associated with these devices. There are over 1,000 TVT studies, over 150 randomized controlled trials on TVT and TVT-O, and multiple meta-analysis. No other incontinence procedure has been as well studied as TVT and TVT-O.
- The FDA's 2013 statement "Considerations about Surgical Mesh for SUI." This statement, noted that the "safety and effectiveness of multi-incision slings is well-established in clinical trials that followed patients for up to one year." It also concluded that out of the potential complications that a patient can experience following pelvic floor surgery, only mesh erosion and extrusion were unique to a synthetic mesh procedure.[1]
- My education, training, and surgical experience, which I've described above. This experience also includes a large number of patients I've treated who have been implanted with slings by doctors other than myself.
- My attendance at different medical conferences and professional society meetings. This includes infomration about the performance of TVT and TVT-O in the hands of a wide variety of pelvic floor surgeons.

[1] The relevant portion from the FDA's 2013 statement reads: "The most common complications reported through MDRs for surgical mesh slings for SUI repair, in descending order of frequency, include: pain, mesh erosion through the vagina (also called exposure, extrusion or protrusion), infection, urinary problems, recurrent incontinence, pain during sexual intercourse (dyspareunia), bleeding, organ perforation, neuro-muscular problems and vaginal scarring. Many of these complications require additional medical intervention, and sometimes require surgical treatment and/or hospitalization. With the exception of mesh erosion, the above complications can occur following a non-mesh surgical repair for SUI."

- My training of other pelvic floor surgeons in treating SUI with TVT and TVT-O. This training provides me with a venue where I have received a lot of feedback about the risks and complications associated with TVT and TVT-O from other pelvic floor surgeons across the country.

Further, I have reviewed numerous IFUs for a significant number of products from various medical device manufacturers, and I can confirm that the warnings in Ethicon's TVT and TVT-O IFU are adequate and consistent with other IFUs from other sling manufacturers.

The Instructions for Use (IFU) for the TVT and TVT-O were appropriate and adequate The IFU is intended to offer information to an experienced gynecological surgeon who is already trained in the surgical treatment of stress urinary incontinence and, more specifically, TVT and TVT-O. It cannot, and is not, intended to take the place of medical school or surgical training. The instructions are intended for general use of the product. Variations in use may occur in specific procedures due to individual technique and patient anatomy. The instructions, therefore, including listed contraindications, warnings and precautions, are intended to be read in light of prior surgical knowledge. The TVT professional education system was extensive and I personally participated and helped educate other surgeons on numerous issues such as surgical technique, placement, complications and complication management. Technical issues regarding placement were covered in numerous modalities in the curriculum, from tips and tricks to practice pointers to surgical videos to powerpoint presentations to cadaver labs to proctoring and precepting.

Claims made by the plaintiff's expert that Ethicon was required to warn surgeons that an operation in the vagina, including the TVT and TVT-O, could result in things like pelvic pain, dyspareunia, scarring, and vaginal shape changes, all of which can be permanent, are unfounded for the reasons I've set forth above. Further, the allegation that Ethicon was required to warn surgeons that revision might be necessary, that a permanent implant may be difficult to remove and that revision might not alleviate symptoms is meritless. The incidence of dyspareunia due to the TVT and TVT-O sling is less than 1% as shown by Tomasselli (65).

All surgeons performing vaginal surgery, including the TVT or TVT-O, are expected to be well aware of these known potential surgical complications. Ethicon identified the correct adverse events and warnings for the TVT and listed them in the IFU and further they were addressed in Professional education and they were widely publicized in peer reviewed and other literature and publications as well. Data associated with the TVT which was widely studied, including efficacy, complication and reoperation rates, were widely available and well known to surgeons performing vaginal surgery.

TVT PATIENT BROCHURE

I have reviewed the patient brochure and the adequacy and appropriateness of the brochure, as well as applicable marketing documents. The patient brochure is typically to facilitate a conversation with the patient and the physician. The patient brochure is not to be the sole piece of data that a patient makes her decision, but what is most critical is the discussion between the patient and the physician to discuss the physician's success rates in his/her hands with the patient's individual factors.

TVT IS NOT CYTOTOXIC AND THE MESH DOES NOT CAUSE MALIGNANCY

Despite extensive use of the polypropylene mesh in humans over decades, concerns have been raised recently about synthetic midurethral slings and a possible link with malignancy(71). These concerns are based on rodent models that demonstrated a high rate of sarcoma formation after subcutaneous implantation of polypropylene. However, further investigation suggests that the risk of malignancy may be related to the surface area and morphology of the implanted material more than to the composition of the material, when sheets of polypropylene were implanted into mice and rats. Perforated materials have been shown to have a lower risk of malignancy.

Much research has focused on the mechanism of tumor formation and has suggested that the composition of the material is not as important as the surface area and morphology of the implanted material in regards to tumor formation. This is known as the Oppenheimer effect. Others have also cautioned against extrapolating from animal studies because "such tests are rarely predictive of performance in humans. There are many examples in which animal studies are highly misleading with respect to clinical safety and efficacy in humans."

Nonetheless, further animal studies using mesh forms of polypropylene have not shown development of sarcomas. Witherspoon et al implanted polypropylene mesh into rodents and monitored the animals for 2 years based on the previously established latency period for malignancy in rodents. No sarcoma developed.

Thus far in the literature, no malignancy associated with polypropylene mesh has been reported in humans.

Tens of millions of polypropylene mesh hernia units have been sold since the 1980s. Over 3 million polypropylene midurethral slings have been sold since the mid 1990s and hundreds of thousands of transvaginal mesh units have been sold in the last 10 years. To date, no mesh site cancers have been reported. Polypropylene mesh: evidence for lack of carcinogenicity (70).

No clinical evidence exists supporting the idea that the Prolene mesh used in TVT™ and TVT-O™ is cytotoxic and causes cell death in vivo, or is associate with malignancy that causes an increase in complications or a decrease in efficacy. There are no reported cases of TVT being causally linked to any cases of cancer (70,72,73).

TVT MESH DOES NOT FRAY, CURL, ROPE NOR IS THERE PARTICLE LOSS

I have explanted portions of the TVT mesh for indication of exposure several years after its initial placement and I have not seen any migrating particles or mesh that was degraded based on an observation at surgery. If any surface cracking or alleged degradation is going to be observed, it would be misleading to suggest that one could see signs of degradation that require SEM imaging or analytical tests to visualize or confirm. In my experience with implanting and explanting TVT mesh, I have not seen loose particles, fraying, or degraded mesh.

I have seen company documents and certain published articles that refer to laser cut meshes as being stiffer which could cause more complications such as erosions, however this has never been substantiated in published literature nor have I seen in my clinical practice of over 400 cases of TVT and TVT-O implantations.

TVT mesh under normal physiologic conditions and stresses does not fray or stretch. However any mesh if subject to undue tension is going to stretch as it has to show some flexural mobility. So, I am aware of the plaintiff's experts showing slides of fraying of the sling mesh but the tension applied is not physiological. Moreover, even when I have gone back to do sling plications for persistent incontinence, I have never see the sling get frayed.

I am aware of an Ethicon company document (74) that showed that at physiologic tensions, the mechanical and laser cut mesh behave similarly and there is no stretching or fraying. At higher tension, this may happen but this is artificial and not natural.

TVT MESH DOES NOT DEGRADE

Polypropylene is a stable and well-accepted biomaterial with a history of over five decades of use in mesh implants. In recent years, concerns regarding implanted polypropylene degradation have been raised as a result of very high magnification SEM images that show portions of some explanted synthetic meshes with “cracked” surfaces. These surface changes were further hypothesized to lead to adverse clinical outcomes, though this is not supported by the extensive peer-reviewed literature related to polypropylene mesh repairs. Prospective studies have followed patients with implanted mid-urethral slings for 17 years and show excellent durability and safety of the procedure.

The clinical studies (such as Clave’s study) plaintiffs’ experts rely on to suggest in vivo degradation occurs with TVT mesh are flawed and do not confirm in vivo degradation, nor do they show an increase in clinically significant complications caused by degradation, or how much degradation is required to cause harm.

There are several experimental studies in small and large animals showing that the inflammatory response to large pore polypropylene mesh is short lived and is needed for healing. Furthermore, Clavé et al (75) could perform chemical analysis in only 32 of 84 explants,1 which is too small a sample for an appropriately powered study. Clavé et al make several statements that their analysis is unable to confirm the oxidative damage of implanted mesh leading to degradation, including, “Several hypotheses concerning the degradation of the PP are described below. None

of these, particularly direct oxidation, could be confirmed in this study . . . . The [Fourier transform infrared] analysis neither confirmed nor excluded oxidation of the PP in the in vivo environment." (75)

Clavé et al stated in their paper "We did not have the opportunity to analyze vaginal implants from nonpathological situation. Therefore, prediction of normal in vivo material aging or the range of consequences in the clinical state beyond the observed samples is not possible."1 In fact, Clavé et al (75) note that despite exhaustive testing, they cannot explain their findings. They state, "Several hypotheses concerning the degradation of the PP are described. None of these, particularly direct oxidation, could be confirmed in this study."

I have also read plaintiff's experts claims that on implantation the release of hydrogen peroxide and hypochlorous acid from leukocytes continues the oxidative process started during manufacture. They go on to state that this process causes cracking in PP fibers, etc, neglecting to note that this result has not been observed in the absence of infection or erosion, as clearly stated by Clavé et al.

Without any proof they state that bacteria commonly contaminate mesh and introduce "bacterial slime." Prior work reveals that even with tapes sitting in the vagina for 6 to 12 weeks in animals and humans, and even with purulent foreign body induced sinuses, only "mixed organisms" with scant growth or no growth are cultured.(76) The reason for this finding is that bacteria are immediately attacked by leukocytes and macrophages and eliminated, even in spaces less than 5 microns.(77)

The host response to foreign body implantation, also known as the foreign body response, has generally been described to include seven interrelated and overlapping phases including: injury, protein adsorption, acute inflammation, chronic inflammation, foreign body reaction (FBR), granulation tissue formation, and encapsulation (78). This reaction is followed by the creation of collagen III, which in some weeks converts to collagen I, which covers the implanted mesh fibers. All this is beneficial as inflammatory response impedes wound infection during the healing phase.

More importantly, inflammation is a complex process and not only is critical in the initial clearing the wound of debris and necrotic/abnormal cells, but it is equally crucial for tissue remodeling and regeneration. For this reason, it is shortsighted and premature to assume that inflammation related to the implantation of a biomaterial will be associated with poor health outcomes.

TVT mesh does not undergo degradation in vivo. There is no peer-reviewed clinical literature, including randomized controlled trials, that supports the theory that TVT mesh degrades, loses particles, ropes, frays or curls in women over time, or that there are clinically significant risks of degradation. I am not aware of any peer-reviewed published literature that shows any risks or complications associated with theoretical degradation nor am I aware of any professional organizations or content experts who have expressed a concern with degradation associated with TVT mesh. Moreover, I have never seen this in my personal experience using this sling in over 300 cases spanning a period of 8 years.

TVT MESH DOES NOT SHRINK

This has been clearly shown by Nilsson in his 17 year follow up that there was no evidence of voiding dysfunction or obstructive voiding over time. The postvoid residuals did not change. This indicates that the mesh stays as it is and does not shrink.

Also a study done by Lo et al using ultrasound assessment of the TVT sling at 3 year follow up showed that sling shrinkage does not happen. Shrinkage is a misperception as it is the scarring of the tissue around the mesh and not the mesh itself that seems to indicate that the mesh is actually shrinking. However, the weave pattern of the macroporous mesh does not allow shrinkage. Also shrinkage when it applies to prolapse mesh cases, is due to the fact that the prolapse has been corrected and the original distention of the vaginal epithelium from the underlying prolapse is no longer there and hence the vagina conforms to its normal shape. This gives an appearance of shrinkage of tissue.

I have extensively reviewed the medical literature and also based upon my own personal experience of having done over 2000 vaginal mesh cases, I have never read or seen mesh shrinkage.

TVT MESH MAINTAINS ITS MACROPOROUS CONSTRUCTION AFTER IMPLANTATION

I am aware of some reports by the plaintiff's experts that the pores of the mesh collapse due to shrinkage or stretching at the time of placement and hence do not maintain the macroporous appearance.

If the sling is placed correctly then it should be laying flat under the urethra and should not stretch. Though company documents state that the laser cut TVT SECUR mesh has some advantage in this regard, mechanical cut mesh also do well and do not stretch if placed correctly. Whenever I have gone back to either perform a sling plication or excision of an exposed mesh, I have never seen a stretched or collapsed mesh.

If the mesh is stretched this is a technical error. In fact with the TVT SECUR this is unlikely to happen as the inserter is removed by a pull back technique. With the TVT or the TVT-O procedure there is a spacer placed between the urethra and the sling during the plastic sheath removal and this ensures that the mesh is not placed under undue tension. Moreover the mesh pores are over 1 mm and hence for the pores to collapse down to less than 10 microns means that it has been placed under an abnormal tension not found in vivo.

CONCLUSION

It is evident from published medical literature on TVT and TVT-O that the safety profile is very high and the complication risks are very low. Retropubic TVT has become the gold standard. Universally, it has been accepted as the first line surgical treatment for the management of stress urinary incontinence.

The studies on this topic are extensive. There are over 200 randomized clinical trial performed with the retropubic TVT procedure. The trans-obturator sling procedure also has been compared with the retropubic procedure in several randomized clinical trials and found to be equally effective. The complication rates of these 2 procedures are very small. The risk-benefit ratio clearly favors the benefits to the patient for control and cure of stress incontinence.

The TVT and TVT-O mesh—which is identical—is extremely safe and reliable. It does not disintegrate, degrade, fray, curl or rope. The TVT mesh has never been found to be cytotoxic nor carcinogenic.

In my experience of using the TVT mesh in over 1000 cases and also reading of the literature in over millions of women who have been implanted with the TVT mesh, it is very evident that this particular product is safe and effective.

My opinions stated above are to a reasonable degree of medical certainty. I reserve the right to supplement or modify my expert opinion based on the discovery, disclosure and timely provision of new findings.

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EXHIBIT C

UNITED STATES DISTRICT COURT

SOUTHERN DISTRICT OF WEST VIRGINIA

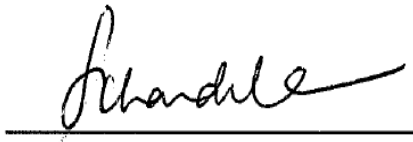
CHARLESTON DIVISION

IN RE: ETHICON, INC., **PELVIC REPAIR SYSTEM** **PRODUCTS LIABILITY LITIGATION**	**Master File No. 2:12-MD-02327** **MDL 2327** **JOSEPH R. GOODWIN** **U.S. DISTRICT JUDGE**

DEFENSE EXPERT GENERAL REPORT

OF SALIL KHANDWALA, M.D.

Prepared by



Salil Khandwala, M.D.

June 3, 2016

GYNECARE TVT SECUR SYSTEM: THE THIRD GENERATION SUBURETHRAL SLING

The following is a designation of my expert opinions for the general report on TVT SECUR SUBURETHRAL SYSTEM . All opinions held by me will be to a reasonable degree of medical certainty and I reserve the right to supplement or modify my expert opinion based on the discovery, disclosure and timely provision of new findings. My opinions in this report are based on my critical review of TVT SECUR that I have implanted in hundreds of women, my extensive clinical experience implanting of over a thousand polypropylene midurethral slings, my education, subspecialty training, analysis of my own clinical trials, reading of the peer-reviewed medical literature, discussions with colleagues, my assessment of the anatomy and the function of devices in clinical surgery, and my Professional Education and experience in teaching the procedure in cadaver labs and on real surgical case proctorships. Based on all of this experience, I can testify up to a reasonable degree of medical certainty.

My *curriculum vitae* is attached, which includes a list of publications I have authored especially in the field of midurethral slings. A complete list of materials reviewed in forming my opinions is attached.

My hourly rate is $500.00 per hour. In the last four years, I have testified in the following cases:

Dina Sanders Bennett v. Ethicon, Inc., et al.; In The United States District Court For The Southern District Of West Virginia Charleston Division; Case No. 2:12-cv-00497

Pamela Free v. Ethicon Inc. et al.; In The United States District Court For The Southern District Of West Virginia Charleston Division; Case No. 2:12-cv-00423

Barbara Kaiser et al. v. Ethicon, Inc. et al.; In The United States District Court For The Southern District Of West Virginia Charleston Division;Case No. 2:12-0887

Beverly Kivel v. Ethicon, Inc., et al.; In The United States District Court For The Southern District Of West Virginia Charleston Division; Case No. 2:12-cv-0-591

Shirley Walker, et al. v. Ethicon, Inc., et al.;In The United States District Court For The Southern District Of West Virginia Charleston Division; Case No. 2:12-cv-00873

Brenda Riddell et al. v. Ethicon, Inc. et al. .;In The United States District Court For The Southern District Of West Virginia Charleston Division; Case No. 2:12-cv-00547

I. BACKGROUND AND EDUCATION

I received the Bachelor of Medicine and Surgery (M.B.B.S) in 1985 from the University of Bombay, India, a residency in Obstetrics and Gynecology (M.D.- Ob Gyn) in 1990 from Bombay, India and from the Greater Baltimore Medical Center in 1997, a fellowship in

Operative Laparoscopy and Hysterectomy in 1993 from the University of Clermont Ferrand, France , and a fellowship in Urogynecology, Reconstructive Pelvic Surgery and Operative Endoscopy in 1998 from the Greater Baltimore Medical Center/University of Maryland. I am board-certified in obstetrics and gynecology.

I am board-certified in FPMRS. I, in fact, was part of the first group that got certified once this subspecialty became credentialed.

I have taught as an Assistant Professor in the Division of Urogynecology and Pelvic Reconstruction Surgery department at the University of Maryland from 1998-2002. I am currently an Associate Professor in the department of Obstetrics and Gynecology at Wayne State University School of Medicine.

I am currently the Director of Female Pelvic Medicine and Reconstructive Surgery at Beaumont Hospital System - Oakwood campus in Dearborn, Michigan. I have been in the practice treating women's health issues since 2000. Specifically, I have treated women with Urinary Incontinence and Pelvic Organ Prolapse since 1997. I, earlier in my career, used the Burch colposuspension (both laparoscopic and laparotomy/open) and fascia lata and rectus fascial slings to treat SUI. Since TVT and mid-urethral slings came to the market they have been my choice for SUI repair especially after reading the extensive literature on this, notably the Hilton and Ward study(1).

I have performed over 2000 SUI surgeries, and have performed approximately 100 TVT slings, 400 TVT-O slings, 300 TVT SECUR procedures and several other midurethral sling operations. I continue to perform these procedures and instead of the TVT SECUR, I perform a similar single incision sling. The only reason I am not performing the TVT SECUR is because it has been removed from the market to my chagrin as I was enjoying excellent personal results. With regards to pelvic organ prolapse (POP) I have been managing this condition since 1997. I have used the following methods to repair POP: native tissue repairs including fascial plications such as anterior/posterior repairs, paravaginal repairs, McCall culdoplasty, sacrospinous ligament suspension, abdominal sacrocolpopexy, uterosacral ligament suspension, colpocleisis. I have also performed augmented prolapse surgery using the IVS Tunneller system, Prolift system, the Prolift + M system, the American Medical System (AMS) Elevate system, the Exair (Coloplast) system, the Restorelle system. I spend 90% of my time taking care of women with issues of the pelvic floor mainly, SUI and POP repair.

I am an investigator with the Urinary Incontinence Treatment Network (UITN) and the Pelvic Floor Disorders Network (PFDN)- two pivotal divisions involved with Female Pelvic Floor conditions at the National Institute of Health (NIH).

As part of the Urinary Incontinence Treatment Network, I was a co-investigator of several keystone sling projects. The first one was the SISTr project that compared Burch colposuspension to the fascial sling procedure. I was also part of a multicenter group who designed, implemented and published the largest US comparative effectiveness trial comparing transobturator midurethral sling to the gold standard retropubic midurethral sling (the TOMUS trial). This landmark study showed the efficacy and safety of both suburethral slings.

I have also taught courses in female pelvic surgery domestically and also travelled nternationally to France, Belgium and India to teach these surgical procedures.

I have conducted several clinical trials of my own and have several papers published especially in the field of urinary incontinence and genital organ prolapse. I have been part of single center studies, multi-centric studies and also international collaborative trials.

II. Board Certification:

Board certification is a voluntary process that demonstrates a physician's expertise in a particular specialty. In addition, the American Board of Medical Specialties [ABMS (parent board to ABOG and ABU)] requires that all certified physicians engage in on-going maintenance of certification to ensure that they stay current of advances in the evaluation and treatment of patients by that specialty.

The ABMS officially approved the specialty of **Female Pelvic Medicine and Reconstructive Surgery** in the spring of 2011. In so doing, ABMS acknowledged that care for women with complex pelvic floor disorders (such as urinary and fecal incontinence, and pelvic organ prolapse) requires subspecialty training and certification beyond the training acquired by a general obstetrician-gynecologist or a general urologist. In June of 2013, the American Board of Obstetrics and Gynecology and the American Board of Urology certified the first individual physicians. I was part of that group to be certified in FPMRS at the first attempt.

I am a fellow of the American College of Obstetrics and Gynecology (FACOG). I am also a member of the American Urogynecologic Society (AUGS).

TEACHING EXPERIENCE

I have trained over 100 Obstetrics and Gynecology residents and two Female Pelvic Medicine and Reconstructive Surgery (FPMRS) fellows. At any given time, there are 2 Ob Gyn residents working with me. I am the primary Urogynecology and FPMRS faculty for the Ob Gyn residents of Oakwood, Wayne State University, Botsford and the Genesys residency programs in Southeast Michigan. I am also the Program Director of a board-certified fellowship in FPMRS. I have had 2 FPMRS fellows. The fellow training tenure spans three years which includes basic science, clinical application and scientific research.

SEMINAL CLINICAL TRIALS THAT I WAS INVOLVED WITH AS A CO-INVESTIGATOR OF UITN

In 2000, the National Institutes of Diabetes, Digestive and Kidney Diseases (NIDDK) established the **Urinary Incontinence Treatment Network** (**UITN**), recognizing the need for well-designed outcomes studies for urinary incontinence treatment in women as previous studies had methodological flaws and/or limitations that precluded definitive conclusions about the relative efficacy or differences in complications between procedures. (UITN. Urology 2005). Randomized controlled trials or comparative effectiveness trials are considered the best of all research designs because the act of randomizing patients to receive one intervention or the other ensures that, on average, all other factors are equal between the groups. Therefore, any significant differences in outcomes or complications between the groups can be attributed to the intervention or procedure and not to some other factor.

Stress Incontinence Surgical Treatment Efficacy Trial (SISTr): In the first trial, Burch and bladder neck slings were selected for comparison by the UITN since they were considered the 'gold standard' procedures for treating stress incontinence in the US at that time; although expert opinion existed regarding the efficacy of the procedures, no prospective comparative data was available to support or refute "expert opinions". We now have 2-year and 5-year outcome and complication data directly comparing these two procedures (2). In this multicenter RCT of 655 women followed for 24 months, success (defined as no self-reported symptoms of SUI, a negative stress test and no retreatment for SUI) was higher in the pubovaginal sling group than the Burch colposuspension group (66% versus 49%; P <0.001). However, pubovaginal slings were associated with an increased risk of UTI (48% versus 32%; P <0.001), voiding dysfunction (14% versus 2%; P <0.001), and postoperative urge incontinence requiring treatment (27% versus 20%; P = 0.04).

Extended Stress Incontinence Surgical Treatment Efficacy Trial: The extended 5 year results published by our group in 482 patients (73.6% of the initial cohort) found that continence rates had decreased substantially in both groups.

Trial of Midurethral Sling (TOMUS) study (4): This study assessed the outcome of 597 women randomized to undergo either retropubic (n = 298) or transobturator (n = 299) midurethral sling insertion. Self-reported symptoms, urinary stress tests, pad tests and retreatment rates were assessed. Objective success rates (defined as a negative provocative stress test, a negative 24 h pad test and no retreatment for SUI) at 12 months were 80.8% in the retropubic group and 77.7% in the obturator group (3% difference, 95% CI 3.6–9.6). Statistical analysis demonstrated equivalence for both procedures in objective measures; however, retropubic slings performed slightly better subjectively (62.2% versus 55.8%; 6.4% difference, 95% CI 1.6–14.3).

OVERVIEW OF STRESS URINARY INCONTINENCE

Prevalence rates

The International Continence Society (ICS) defines urinary incontinence as ‘‘the complaint of any involuntary leakage of urine,’’ providing a good clinical definition for patient evaluation(5).

A review of 21 studies by Thom(6) revealed that the pooled mean prevalence for older women was 34% for any incontinence and 12% for daily incontinence. Among middle-aged and younger adults, the pooled mean prevalence was 25%. Stress incontinence was more common in younger women, whereas urge and mixed incontinence was more common in older women. In 3 large, multinational, population-based studies, the prevalence of lower urinary tract symptoms ranged from 59.2% to 76.3%, but the prevalence of actual incontinence ranged from 9.3% to 14.8% (7-9). A large epidemiologic study of community-dwelling women in the United States by Lukacz and colleagues (10) reported that women with frequent daytime or nighttime voiding had twofold higher bother scores compared with unaffected women, and that increases in voiding frequency incrementally increased patient bother. This finding highlights the point that many women have bothersome symptoms even though they do not have incontinence.

Race and age on incontinence prevalence

Nygaard and colleagues(11) found no differences in prevalence rates between Hispanic, non-Hispanic whites, non-Hispanic blacks, and other races, whereas Dooley and colleagues (12) found that white and Mexican American women had almost double the prevalence rates for stress incontinence compared with blacks, but blacks had a higher rate of urge incontinence (11% compared with 7.5% for white and Mexican American women).

Thom and colleagues (13) specifically evaluated differences in incontinence prevalence among major race and ethnic groups in the Reproductive Risks of Incontinence Study at Kaiser (RRISK) and found that the prevalence for all types of incontinence was highest in Hispanic women (36%), followed by white (30%), black (25%) and Asian American (19%) women. Additional analysis from the RRISK suggests that incontinence is significantly associated with a decrease in quality of life, and this effect does not vary significantly by race (14).

The Establishing the Prevalence of Incontinence (EPI) study focused on comparing incontinence prevalence between white and black women. In this study, Fenner and colleagues (15) reported that a significantly higher proportion of white women reported stress incontinence compared with black women (39.2% vs 25%, respectively), whereas a greater proportion of black women reported urge incontinence compared with white women (23.8% vs 11%, respectively).

In contrast to previous studies (16), the EPI study showed that, other than race, risk factors for incontinence were similar between black and white women, including increased age, mobility

impairment, constipation, obesity, and depressive symptoms. Nygaard and colleagues reported that the prevalence of incontinence in women in the United States over the age of 80 years was 31.7% compared with women aged 40 to 59 years with a prevalence of 17.2%.

Urinary incontinence costs

The financial burden of incontinence includes direct and indirect costs. Direct costs include routine care (absorbent products and laundry), medical visits and treatments, and treatment complications or failures. Indirect costs are more difficult to estimate, and include loss of productivity and costs of paid or unpaid caregivers. Although unable to estimate a cost associated with loss of productivity, the study showed that 23% of incontinent women missed an average of 28.7 hours of work for inpatient and outpatient care. It is estimated that for stress incontinence, direct costs of medical care for surgical patients without comorbidities was $13,212 per patient (17). Subak and colleagues (18-20) provided more accurate estimates of the individual economic costs for routine incontinence care. The annual direct cost of routine care ranged from $250 to $900 in 2005 dollars per woman (18-20).

Predisposing factors

In a twin study by Altman and colleagues (21), genetic effects seemed to contribute to stress incontinence and pelvic organ prolapse, but the influence of environmental factors was also substantial.

Inciting factors

Inciting factors are those that likely could be modified, but often cannot be avoided. Although most parous women do not have pelvic floor dysfunction, one major inciting factor for pelvic floor dysfunction is childbirth. Similarly, in the RRISK cohort, Rortveit and colleagues (22) found that the risk of prolapse was significantly increased in women with 1 (odds ratio [OR] 2.8, 95% confidence interval [CI] 1.1–7.2), 2 (OR 4.1, 95% CI 1.8–9.5), and 3 or more (OR 5.3, 95% CI 2.3–12.3) vaginal deliveries compared with nulliparous women.

Promoting factors

In addition to chronically increased intra-abdominal pressure, neurogenic disease caused by obesity may place obese women at greater risk for prolapse and incontinence.(23) Obesity has been shown to be a risk factor for urinary incontinence(24). Subak and colleagues (25) conducted a randomized clinical trial, the Program to Reduce Incontinence by Diet and Exercise (PRIDE), and found that a 6-month behavioral intervention targeting weight loss reduced the frequency of self-reported episodes of urinary incontinence among overweight and obese women

compared with a control group. Burgio and colleagues (26) reported that, in incontinent women losing 18 or more BMI points after bariatric surgery, 71% regained urinary continence at 12 months.

Higher BMI has also been associated with pelvic organ prolapse. In one study, women with type 1 diabetes had a nearly twofold greater prevalence of weekly urge incontinence compared with women without diabetes (8.8% vs 4.5%) (27) . Using data from the Action for Health in Diabetes (Look AHEAD) study evaluating overweight and obese women with type 2 diabetes, Phelan and colleagues reported that weekly incontinence (27%) was reported more often than other diabetes-associated complications including retinopathy (7.5%), microalbuminuria (2.2%), and neuropathy (1.5%).

The large EPICONT study reported that former and current smoking was associated with incontinence, limited to those women who smoked 20 cigarettes a day or who had a 15 year pack history(28). It may be postulated that increased prevalence of incontinence among smokers is secondary to strong and frequent coughing, and therefore increased intra-abdominal pressure. Other theories regarding smoking and its effect on incontinence include the negative effect of smoking on estrogen, and possible interference with collagen synthesis. The prevalence of urinary incontinence in older, postmenopausal women was also found to increase almost twofold with COPD (29).

Certain medications may predispose women to pelvic floor disorders secondary to their mechanism of action (eg, by lowering bladder outlet resistance).Other drugs may predispose women secondary to side effects (eg, constipating medications or cough-inducing medications). Drugs that may predispose women to incontinence include a-adrenergics, angiotensin-converting enzyme (ACE) inhibitors, antipsychotics, benzodiazepines, and antidepressants. The role of hormone therapy on incontinence symptoms has been evaluated (30). Using data from the WHI, Hendrix and colleagues (31) reported that menopausal hormone therapy increased the incidence of all types of urinary incontinence at 1 year among women who were continent at baseline. The risk for stress incontinence was 1.87 and 2.15 fold higher for women on estrogen and progesterone therapy or estrogen therapy alone, respectively, compared with controls.

The risk for mixed incontinence was 1.49-and 1.79-fold higher for women on estrogen and progesterone therapy or estrogen therapy alone, respectively, compared with controls. In a case control study, Arya and colleagues (32) found a 2.5-fold higher risk of detrusor overactivity in women with high caffeine intake and after controlling for age and smoking.

PHYSIOLOGIC NEUROANATOMY OF URINE STORAGE AND EVACUATION

Anatomy: Bladder

The base of the bladder includes the vesical trigone, which is bounded by the two ureteral orifices and the internal urethral opening. An important distinction between the dome and the base is the type of neurotransmitter receptor that predominates. At the dome, beta-adrenergic and cholinergic receptors predominate, whereas alpha-adrenergic receptors predominate at the base and the proximal urethra. The primary cholinergic (muscarinic) receptor subtypes in the human bladder are M2 and M3. Although there are more M2 receptors, the M3 receptors predominate in the mediation of detrusor contraction.

Anatomy: Urethra

Surrounding the mucosal lining of the urethra is a submucosal layer that contains a prominent vascular plexus. This plexus is thought to contribute to the watertight closure of the urethral lumen. Adjacent to the submucosal layer lie two layers of smooth muscle: a well-developed inner longitudinal and a poorly defined outer circular layer. The most external layer of the urethral wall consists of the striated urogenital sphincter muscles (see Fig 1). This complex consists of the sphincter urethrae and two strap like bands of muscle, the urethrovaginal sphincter and compressor urethrae muscles (Fig 2).

Peripheral nervous system

The superior hypogastric plexus primarily contains sympathetic fibers from the T10 to L2 cord segments and terminates by dividing into right and left hypogastric nerves. The inferior hypogastric plexus, also known as the pelvic plexus, is formed by visceral efferents from S2 to S4, which provide the parasympathetic component by way of the pelvic nerves. The somatic component of the peripheral nervous system that is relevant to lower urinary tract function takes origin from Onuf's somatic nucleus. Onuf's nucleus, located in the ventral horn of the gray matter of S2 through S4, contains the neuronal cell bodies of the fibers that supply the striated urogenital sphincter complex.

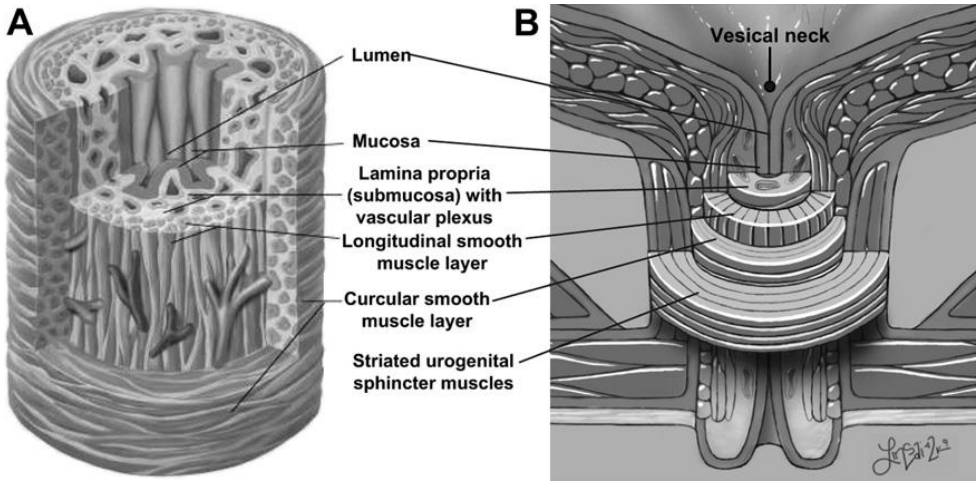


Fig. 1 Courtesy of Lindsay Oksenberg, Dallas, TX).

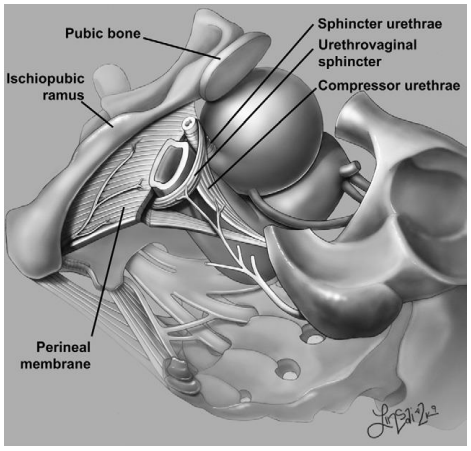


Fig 2 Striated urogenital sphincter anatomy (Courtesy of Lindsay Oksenberg, Dallas, Texas).

Neurophysiology

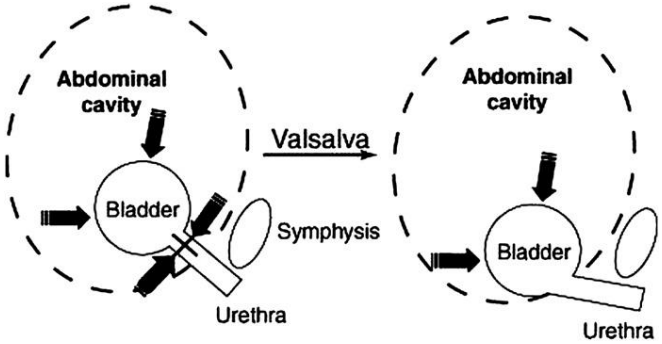
Activation of the urethral motor neurons in Onuf's nucleus results in contraction of the striated urogenital sphincter muscles by way of the pudendal nerve. Simultaneously, activation of the spinal sympathetic reflex (T11–L2) by way of the hypogastric nerves results in alpha-adrenergic contraction of urethral smooth muscle with increased tone at the vesical neck and inhibition of parasympathetic transmission, which inhibits detrusor contraction. The net effect is that urethral pressure remains greater than detrusor pressure, facilitating storage.

PATHOPHYSIOLOGY OF STRESS URINARY INCONTINENCE

Early Anatomic Theories

Kelly used his cystoscope to describe SUI, reporting that "the cystoscopic picture presents a gaping internal sphincter orifice which closes sluggishly." He attributed SUI to "vesical neck funneling," which he hypothesized was caused by loss of elasticity or normal tone of the urethral and vesical sphincter. In 1923, Bonney stated that "Incontinence appears to be due to laxity of the front part of the pubo-cervical muscle-sheet, so that it yields under sudden pressure and allows the bladder to slip down behind the symphysis pubis and the urethra to carry downwards and forwards by wheeling round the sub-pubic angle."

Pressure Transmission Theory (Enhorning)



Stress urinary incontinence: the pressure-transmission theory. (From Wai CY. Urinary incontinence. In: Schorge JO, Schaffer JI, Halvorson LM, et al, editors. Williams Gynecology. 1st edition. New York: McGraw Hill Medical; 2008. p. 518)

Enhörning developed a urethral catheter with 2 pressure transducers 5 cm apart, which permitted simultaneous measurement of vesical and urethral pressures. Using this apparatus, he showed that, in continent subjects, urethral pressure exceeded vesical pressure, both at rest and during increases in intra-abdominal pressure. He hypothesized that this equal rise in vesical and urethral pressure was due to transmission of intra-abdominal pressure to the bladder and the part of the proximal urethra above the pelvic floor. The transmitted intra-abdominal pressure maintained continence by keeping the urethral pressure differentially higher than the bladder pressure. Conversely, "In cases of stress incontinence this upper part of the urethra is often relaxed and the increase in the intra-abdominal pressure does not get transmitted to the urethra."

DeLancey's Hammock hypothesis

In 1996, DeLancey proposed a consolidated theory of SUI. Using anatomic research, he hypothesized that the pubocervical fascia provides hammock-like support for the vesical neck and thereby creates a backboard for compression of the proximal urethra during increased intra-abdominal pressure. Loss of this support would compromise equal transmission of intraabdominal pressure. This part of DeLancey's theory combines the theories of Bonney and Enhörning. However, his theory also accounts for neuromuscular dysfunction. DeLancey's anatomic observations showed a connection of the pubocervical fascia with the insertion of the levator ani muscles at the symphysis pubis. He hypothesized that this connection with the levator ani muscles permits active elevation of the vesical neck during contraction of the levator ani muscles. This part of the theory provides a mechanism for SUI due to neuromuscular injury.

The Integral Theory

Petros and Ulmsten proposed the integral theory of urinary incontinence. This theory attempts to account for the interplay of the structures involved in female urinary continence, as well as the effects of age, hormones, and iatrogenically induced scar tissue. The investigators hypothesized that stress and urge symptoms both derive, for different reasons, from anatomic laxity in the anterior vaginal wall. The laxity may be caused by defects in the vaginal wall itself or in the ligaments and muscles that support it. According to this theory, the vaginal wall has a structural function that prevents SUI by transmitting the muscle movements involved in bladder neck

opening and closing, as well as a function that prevents urgency by supporting hypothesized stretch receptors located in the proximal urethra and bladder neck.

Ideal support requires intact and healthy (1) ligaments along the lateral aspects of the urethra, termed the pubourethral ligaments; (2) anterior vaginal wall and its lateral fascial condensation; (3) arcus tendinous fascia pelvis; and (4) levator ani muscles. Collectively, this support provides a firm backboard against which the urethra is supported during increases in intra-abdominal pressure thereby maintaining continence. The proximal two-thirds of the urethra and bladder neck is fused to the anterior vaginal wall, relying greatly on this attachment for support.

Urethral Sphincteric Dysfunction theory

Using a rat model, Kamo and colleagues demonstrated active a closure mechanism in the mid urethra. The investigator used microtip transducer catheters in the proximal and mid urethra to evaluate the urethral closure mechanism under stress conditions induced by sneezing. They noted that, during sneezing, pressure readings increased in the proximal and mid urethra but not in the distal urethra. The response in the proximal urethra was almost negligible when the bladder response was subtracted, suggesting that the proximal urethra closed by passive transmission of increased abdominal pressure. Conversely, the mid-urethral response was still observed after subtracting bladder response, suggesting that the mid urethra closed by an active contraction mechanism in addition to the passive mechanism of the proximal urethra. Moreover, in the mid urethra, the active urethral closure pressure was not related to the magnitude of bladder response, and the urethral response began before the bladder response.

The motor neurons of the external urethral sphincter are located in the ventral horn of the lumbosacral spinal cord in Onuf's nucleus. Stimulation of these neurons evokes contractions of the external urethral sphincter. The external urethral sphincter reflexes are enhanced by serotonin agonists and depressed by serotonin antagonists, suggesting that the descending serotonergic pathways are responsible for the spinal cord circuitry controlling the closure mechanism of the external urethral sphincter.

NON-SURGICAL TREATMENT FOR STRESS URINARY INCONTINENCE

A. Pelvic Floor Muscle Therapy

This typically involves some method of biofeedback whether it is with e-stimulation or with weighted cones. It needs significant motivation on part of the patient and the results are not instantaneous. With the e-stimulation version, a vaginal probe is used for stimulation of the pelvic floor muscles whereas the rectal probe is used to assess the spontaneous contractions of the pelvic floor. This therapy is done on a weekly basis for about 4-6 weeks and was to sessions been done every couple of months. Approximately half of women with stress predominant urinary incontinence are satisfied one year after starting pelvic floor muscle training.

B. Incontinence Pessaries

Incontinence pessaries are used for patient with stress incontinence mainly as a temporary basis. They could be used in women who are pregnant or desirous of pregnancy. It essentially has a knob that sits under the urethra and causes some degree of urethral compression thereby increasing the urethral resistance.

Sometimes, patients may use a tampon in the vagina however this acts as an absorbent rather than provide a true urethral compression. Urethral plugs have also been used but these should be used temporarily when a patient has just a short bout of incontinence. One randomized trial demonstrated similar satisfaction with stress incontinence symptoms one-year after pessary and behavioral-physical therapy (35) .There was no benefit to combined therapy with pessary and behavioral-physical therapy.

C. Behavioral Modification

Timed voiding is an integral component for the management of urinary stress incontinence. If a woman is going to the bathroom very infrequently, then going to the bathroom every 2-3 hours would help decrease the bladder volume and therefore urinary incontinence. Patient could also be encouraged to empty the bladder prior to engaging in any strenuous activities.

Women should also be informed about the amount of fluid intake and use of caffeinated beverages as these would increase the amount of urine production and bladder volumes. Obesity is an independent risk factor for the development of incontinence, with obese women having a 4.2-fold greater risk of stress urinary incontinence than those with a normal body mass index. Several trials demonstrate that moderate weight loss can improve stress urinary incontinence symptoms in overweight and obese women suggesting that even moderate weight loss can improve stress urinary incontinence.

D. Urethral Bulking Agents

Bulking agents were popularized by the transurethral injection of collagen. This could be done transurethrally or periurethrally. It is mainly indicated in patients who have a fixed urethra without mobility. These patients are unlikely to be benefited by a suburethral sling procedures as the sling would have to be obstructive. Transurethral bulking procedures could also be complimentary to a sling procedure when the patient has noticed improvement but not complete cure. There are different types of agent used such as Macroplastique, Durasphere. Collagen is no longer available.

SURGICAL TREATMENT FOR STRESS URINARY INCONTINENCE

Anterior colporrhaphy

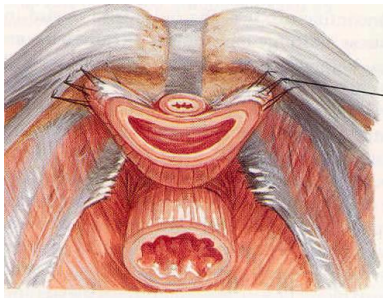
A meta-analysis of eight randomized trials comparing anterior colporrhaphy to other open retropubic techniques demonstrated a higher subjective failure rate for anterior colporrhaphy than for open Burch colposuspension in both the short term (29% versus 14% within 12 months; RR 1.89, 95% CI 1.39–2.59) and long term (41% versus 17% after 12 months; RR 2.50, 95% CI 1.92–3.26). (36)

Needle suspension surgery : Raz and Stamey procedures

A meta-analysis of 10 trials comparing needle suspension techniques to open Burch colposuspension demonstrated a higher failure rate in the needle suspension group (34% versus 23%; RR 0, 95% CI 1.5–2.7). (36)

BURCH COLPOSUSPENSION

The Burch procedure involves attaching the periurethral fascia to the iliopectineal ligament with multiple sutures to stabilize the urethra. The stitches are placed in the space of Retzius and incorporate the fascia overlying the anterior vaginal wall on either side of the bladder neck Traditionally 2 sutures are placed on each side of the bladder neck and attached to the ilio-pectineal (Cooper's) ligament. A suture bridge is maintained in order to prevent excessive overcorrection.



Alcalay et al followed 366 women who underwent colposuspension between 1974 and 1983 and invited them to attend the urogynaecology unit for a 10 to 20 year follow up in January 1994. 109 subjects participated in this study. Objective cure was defined as inability to demonstrate stress incontinence during clinical examination and provocative urodynamics. They observed that cure rate of stress incontinence is time dependent and therefore survival analysis is an appropriate method to evaluate long term results. Alcalay et al. (37) found that the cure of incontinence following Burch colposuspension was time-dependent, with a decline for 10–12 years when a plateau was reached. at 69%. The most frequent complication of colposuspension in this series was de novo detrusor instability (14· 7 %).

Kjølhede (38) did a follow up of 190 women who underwent open Burch colposuspension and demonstrated significant urinary incontinence in 56% of patients at 14 years, while only 19% of women remained completely dry.

The cure rate of the Burch colposuspension seemed to decline over time. Burch colposuspension is also associated with significant morbidity; recurrent UTI in 4.6%; de novo detrusor instability in 14.7% of patients; long term voiding difficulty in 22% of patients; high rates of pelvic organ prolapse resulted from the Burch (37% in this study).

A Cochrane review done by Lapitan et al of open retropubic colposuspensions, which included 53 studies (*n* = 5,244), reported an overall success rate of 68.9–88.0%.(39)

Incontinence has also been found to be less common after the open Burch procedure (RR 0.38, 95% CI 0.18– 0.76) than after the MMK procedure between 1-year and 5-year follow-up (RR 0.38, 95% CI 0.18–0.76). This meta-analysis also reviewed 12 trials (*n* = 1,260) comparing open Burch procedure to laparoscopic Burch procedure and found no significant difference in patient-reported incontinence between 1-year and 5-year follow-up (RR 0.97, 95% CI 0.75–1.03).(39)

The long-term success of open Burch colposuspension was demonstrated by Sivaslioglu *et al.*(40) in 262 patients with an 84% success rate at 7 years. However, in the longer term success rates decline. Follow-up of 190 women who underwent open Burch colposuspension demonstrated significant urinary incontinence in 56% of patients at 14 years, while only 19% of women remained completely dry.(38)

Overall, the Burch colposuspension has been documented as a safe and effective surgical option for SUI and can be considered for women undergoing an open abdominal procedure for concomitant surgery (for example, pelvic organ prolapse surgery).

Pubovaginal slings

Pubovaginal sling procedures for SUI were introduced at the beginning of the 20th century and remain a feasible option for the management of SUI. (41)

The pubovaginal sling insertion procedure involves abdominal and vaginal incisions with placement of a fascial sling at the proximal urethra. The ends of the sling are passed through the tunnels into the retropubic space and are fixed to the anterior rectus fascia providing support to the urethra during increased intra-abdominal pressure. Alternatively, a suspended sling-on-a-string method can be used to reduce the invasiveness of the procedure and to shorten the length of sling material required.

Both synthetic (for example, polypropylene) and biologic (autograft [rectus fascia, fascia lata, vaginal skin], allograft [fascia, dermis, dura mater], or xenograft [porcine or bovine]) materials have been used to make pubovaginal slings. In their update on the surgical treatment of SUI from the 4th International Consultation on Urinary Incontinence, Smith *et al.* summarized data from 15 randomized controlled trials (RCTs) reported from 1978 to 2008. Autologous rectus fascia was found to be the most widely evaluated material. However, there was no high-level evidence demonstrating a difference in success rates between biological and synthetic slings. Adverse events were more commonly reported by patients who underwent synthetic sling insertion. (42)

Fascial sling versus Burch randomized clinical study- Stress Incontinence Surgical Treatment Efficacy Trial (SISTr)

The largest trial to date comparing autologous rectus fascia pubovaginal slings to Burch colposuspension was reported by Albo *et al.* in 2007 (2). In their multicenter RCT of 655

women followed for 24 months, success (defined as no self-reported symptoms of SUI, a negative stress test and no retreatment for SUI) was higher in the pubovaginal sling group than the Burch colposuspension group (66% versus 49%; *P* <0.001). However, pubovaginal slings were associated with an increased risk of UTI (48% versus 32%; *P* <0.001), voiding dysfunction (14% versus 2%; *P* <0.001), and postoperative urge incontinence requiring treatment (27% versus 20%; *P* = 0.04). Brubaker et al from the same group (3) published the results at 5 years in 482 patients (73.6% of the initial cohort), the e-SISTr study (extended Stress Incontinence Surgical Treatment Efficacy Trial) and found that continence rates had decreased substantially in both groups. Overall continence rates were higher in the pubovaginal sling group (30.8%, 95% CI 24.7–36.9) than in the Burch colposuspension group (24.1%, 95% CI 18.5–29.7; *P* = 0.002). Patient satisfaction decreased from 2 years to 5 years in both groups (from 87% to 83% in the sling group and from 79% to 73% in the Burch colposuspension group) but remained statistically significantly higher for patients who underwent pubovaginal sling insertion (83% versus 73%; *P* = 0.03). Adverse events were similar in both groups at 24 months (10% in the Burch colposuspension group and 13% in the pubovaginal sling group; *P* = 0.2) and at 5 years (10% in the Burch colposuspension group and 9% in the pubovaginal sling group).

Long-term data support the use of autologous pubovaginal sling surgery in women with SUI, especially those who have failed other procedures, have had urethral mesh complications (such as vaginal or urethral erosion), or who require a concomitant urethral reconstructive procedure, such as repair of urethral fistula, diverticulum, or destroyed urethra.

The origin of the TVT sling

The midurethral slings were placed via a retropubic approach based on the ‘integral theory’ of SUI proposed by Ulmsten and Petros.(43)

They postulated that three structures (the pubourethral ligament, the suburethral vaginal hammock, and the pubococcygeus muscles) are closely integrated in a complicated coordination to open and close the bladder neck and urethra. Defects in one of these structures or in their interaction will result in incontinence or voiding dysfunction. Weakness of the pubourethral ligaments results in the inability to adequately occlude the urethra, which contributes to SUI. Based on these assumptions, Ulmsten and Petros designed a minimally invasive surgical procedure; the retropubic approach was devised to reconstitute the pubourethral ligament and the suburethral vaginal supports.

Ulmsten using the Prolene mesh that was 1 centimeter wide and 40 centimeters long published the results of his clinical trial in 1996, included 75 patients with 2 year follow-up and had 92% of patients cured or significantly improved. There were no tape rejection or defective healing, and no intra-operative or post-operative complications. In the mid-1990s, Ethicon met with Dr. Ulmsten and began working with him to create the retropubic TVT sling.

The Prolene mesh Ulmsten used in his first studies was the same mesh that Ethicon used for all of its TVT products, with the exception that a blue dye was added and it was offered in 2006 with a laser or mechanical cut. I have used both and reviewed literature of both and the results

are identical and there has been no clinical significance to the laser versus mechanical cut mesh in my practice or the literature.

Ethicon contracted with Dr. Ulmsten and Medscand in 1997 to begin the development and sell of TVT in Europe. I have reviewed the contracts and from a medical point of view there is no concern. By 1998, a multi-center trial with six centers was published with 91% of patient's cured and 7% significantly improved. The results were excellent. Ethicon begin selling TVT in Europe in 1997. With the excellent results from the published studies and reports in Europe the product was launched in 1998 in the United States.

By 2001, there was 5 year data on the TVT showing excellence results. In 2002, studies of up to 3 years showed that TVT did not affect sexual function and there were no women who had dyspareunia as a result of the TVT. In fact, women could expect to have their sexual experience to remain the same or be enhanced with the TVT (44). By May of 2003, Dr. Karram, reported on 350 patients with 4 years follow-up. Erosions and nerve injures were less than 1%. It was determined again that the TVT was safe and effective. The studies continued to show that the TVT was safe and effective. Long term data on TVT now exist all the way up to 17 years that show excellent results without any significant deterioration in success.

Tension-free vaginal tape versus colposuspension for primary urodynamic stress incontinence: 5-year follow up (45)

Ward and Hilton reported the 5-year outcomes of their original RCT, at which time 72 patients in the midurethral sling group and 49 of those in the Burch colposuspension group completed objective and subjective testing. Negative pad tests were reported by 81% of the patients with a midurethral sling compared to 90% of those in the colposuspension group ($P = 0.21$). 91% of patients with a midurethral sling and 90% of the Burch group were satisfied with the results of the repairs, as reported using the Bristol Female Lower Tract Symptoms questionnaire. Pelvic organ prolapse was more common in the Burch group than the midurethral sling group (42% versus 23% [$P = 0.026$] for vault prolapse or enterocele; 49% versus 32% [$P = 0.023$] for rectocele), and mesh erosion occurred in four women in the midurethral sling group (three vaginal; one bladder). Reoperation rates for SUI were similar (3.4% for colposuspension and 2.3% for TVT™; $P = 0.74$). Overall, similar success was reported for both procedures at 5 years.

Based on a systematic literature search performed in January 2007, Novara et al (46, 47) reported two systematic reviews and meta-analyses of randomized controlled trials (RCTs) evaluating the efficacy and complication rates of TVT compared with Burch colposuspension, pubovaginal slings, and other midurethral tapes. On the whole, the data from the two meta-analyses suggested that TVT was significantly more effective than colposuspension and was followed by similar complication rates; the data also showed that TVT was similar in efficacy to pubovaginal slings, which are followed by significantly higher perioperative morbidity. Finally, the two meta-analyses demonstrated that TVT and Transobturator slings (TOT) had similar efficacy, although

the risk of bladder perforations, pelvic hematoma, and storage lower urinary tract symptoms (LUTS) was significantly less common in patients treated with TOT

The retropubic sling can be placed via a top-down approach or a bottom-up approach. For the top-down approach, an incision is made in the anterior vaginal wall and the periurethral space is dissected. Trocars are passed through small incisions in the anterior abdominal wall just superior to the pubic bone. The trocar passes retropubically and exits through the dissected periurethral space. The sling (for example, Lynx® [Boston Scientific, USA] or SPARC™ [American Medical Systems, USA]) is then attached to the trocar and the trocars are removed, placing the sling under the midurethra in a tension-free manner. For the bottom-up approach, the trocars are passed vaginally through the dissected periurethral space. They travel retropubically and exit through the anterior abdominal wall superior to the pubic bone. The sling (such as the TVT™ or the Advantage® [Boston Scientific, USA]) is then attached to the trocar and the trocar is removed.

Rehman *et al.* (48) conducted a meta-analysis to determine the outcomes of traditional pubovaginal slings versus other surgical options for SUI, including synthetic midurethral slings. In eight trials including 693 patients they found an equal rate of short-term success (at 12 months) between pubovaginal slings and midurethral slings (RR 0.97, 95% CI 0.78–1.20).

Ogah et al (49) performed a meta-analysis of 62 trials involving 7,101 patients and evaluated the short-term clinical effects of minimally invasive synthetic midurethral sling procedures for the treatment of both urodynamic SUI and clinically symptomatic SUI. Eight RCTs (599 patients) compared synthetic midurethral slings with pubovaginal slings, and the overall subjective cure rate within 12 months was similar between the two (73% vs 71%, RR 1.03, 95% CI 0.94–1.13). However, the midurethral slings are associated with shorter operative times, quicker recovery, and fewer postoperative complications . Rates of new onset urgency and urgency incontinence are lower after midurethral sling compared to bladder neck slings.

In 2010 Novara *et al.* (50) added 14 new trials to their 2007 systematic review and meta-analysis that evaluated the efficacy, complication rate and reoperation rate of Burch colposuspension, pubovaginal slings and synthetic midurethral slings. Only two trials reported follow-up >60 months. Midurethral slings were found to have a higher objective cure rate than Burch colposuspension (OR 0.38, 95% CI 0.25–0.57; P <0.0001) but a similar subjective cure rate (OR 0.79, 95% CI 0.52–1.21; P = 0.27).

One meta-analysis (49) has compared the bottom-up TVT™ and the top-down SPARC™ , and found that women who underwent the bottom-up approach had significantly fewer bladder perforations (4.7% versus 8.5%; RR 0.55, 95% CI 0.31–0.98), fewer vaginal tape erosions (0.7% versus 3.5%; RR 0.27, 95% CI 0.08–0.95), and reported significantly higher subjective (85% versus 77%; RR 1.1, 95% CI 1.01–1.2) and objective cure rates (92% versus 87%; RR 1.06, 95% CI 1.01–1.11). There was no difference in QOL outcomes.

LONG TERM STUDIES ON TVT-- UPTO 17 YEARS FOLLOW UP!

Seventeen years' follow-up of the tension-free vaginal tape procedure for female stress urinary incontinence: C. G. Nilsson (51)

The study population consisted initially of 90 consecutive women diagnosed with primary stress urinary incontinence. Of the women who potentially could have been assessed, 58 out of 74 (78.4 %) were evaluated in some way. Forty-six women were evaluated according to the protocol at the clinics. The mean follow-up was 201 months (16 years and 9 months) with a range between 185 and 213 months. Objective cure, defined as a negative stress test, was seen in 42 out of 46 women (91.3 %). The PGII revealed that 48 out of the 55 women (87.2 %) regarded themselves cured or significantly better than before surgery, 5 out of 55 (9.1 %) experiencing no change and 2 out of 55 (3.6 %) worse than before surgery.

To the question, do you experience leakage during straining, 42 out of 53 (79.2 %) answered no and 50 out of 51 (98 %) would recommend the TVT procedure to a friend. The actual percentage of those lost to follow-up was thus 22 %, which is fairly low for a period of almost two decades. The objective cure rate, assessed by the stress test, was 91 % and showed no decline between 5 and 17 years' follow-up. The corresponding subjective perception of either cure or improvement was over 87 %, with a slight decline during the last 6 years, probably mostly due to urgency incontinence.

Nielsen et al make very keen observations based upon this long term 17 year follow up study:

There seems to be no shrinkage of the TVT mesh over time, as suggested by postvoid residual volumes within normal ranges, except for 2 patients with concomitant diseases (Parkinson's, grade III cystocele).

The mesh complications seen in association with urogenital prolapse surgery that have alerted the FDA might not be caused by the mesh material itself. As long as a type I material is used the complications could be the result of improper training of the surgeon, resulting in an inappropriate surgical technique or choosing the wrong indication or wrong patient for the graft procedure.

The present report suggests that using a type I, macroporous, monofilament, lightweight, and soft polypropylene mesh, the risk of mesh complications even 17 years after implantation under the vaginal mucosa is negligible provided the surgery is performed by a trained and experienced surgeon.

Olsson et al (52) conducted a retrospective long term follow up of 11.5 years following the retropubic TVT procedure. 124 women undergoing TVT have been followed-up 11.5 years post-operatively. In the study group of 104 women, they found an objective cure rate of 84 % according to a negative stress test, while the subjective cure in the whole group was 77 %.

Chugtai (53**)** reviewed a total of 6355 nonpediatric urologists applied for certification or recertification between 2003 and 2012. Two-thirds (4185) reported performing any procedures for female incontinence. Procedures sharply increased from 4632 in 2003 to 7548 in 2004, then remained relatively stable between 2005 and 2012 (range, 8014-10,238 cases). Traditional procedures decreased from 17% of female incontinence procedures in 2003 to 5% in 2004 to <1% since 2010 (P <.0005). Midurethral sling procedures have risen sharply from 3210 procedures in 2003 to 7200 in 2012 (P <.0005). Endoscopic injection treatments have remained stable. Slings comprised of 69% of the female incontinence procedures for SUI in 2003; whereas in 2012, slings increased to 86%.This study which evaluated data from the ABU, showed that midurethral slings and urethral bulking agents are the only procedures performed currently for female SUI, with 5 times as many midurethral slings performed as urethral bulking agents.

A study from 2015 evaluating the IUGA members' practice patterns showed that the preferred method of treatment for SUI is the midurethral sling, regardless of prior treatments, concomitant surgeries, or examination findings (54). "Synthetic midurethral slings are predominant in the current treatment of SUI." "The treatment of stress incontinence has shifted in recent years, with the initial survey showing a predilection for the Burch colposuspension as a primary and secondary surgical treatment for normal pressure urethral SUI (44 and 41%), while the current survey revealed that 2% of respondents were performing the Burch procedure as a primary SUI treatment and 11% of respondents were using it as a secondary treatment." TVT is the preferred treatment for patients with ISD.

TRANSOBTURATOR SLINGS

The transobturator approach was introduced in 2001by deLorme (55) with the aim of decreasing the risks of perioperative bladder, bowel, and vascular complications reported rarely with the retropubic approach. Based on the 'hammock theory' of female SUI proposed by Delancey(33) in 1994, the mesh is placed under the urethra through the obturator membrane and obturator internus muscle in the horizontal plane. The hammock theory states that both urethral support and constriction are necessary for continence and that multiple tissue layers (including the anterior vaginal wall, endopelvic fascia and pelvic floor muscles) are responsible for this support and constriction. Based on this theory, the mesh provides support for the urethra at times of increased intra-abdominal pressure, thus preventing urinary leakage.

Transobturator mesh can be placed via an outside-in approach (Monarc™ [American Medical Systems, USA], ObTryx® [Boston Scientific, USA], Aris [Coloplast, USA]) or an inside-out approach (TVT-O™ [Ethicon, USA], Abbrevo™ [Ethicon, USA]).

First, an incision is made in the anterior vaginal wall and the periurethral space is dissected. For the outside-in approach, the trocar is passed into the inner thigh (a small puncture made inferior to adductor longus tendon at the level of the clitoral hood) through the obturator membrane and exits through the periurethral dissection. The sling is attached and the trocar removed, passing the sling into position. For the inside-out approach, the sling is attached to the trocar, which is

passed from the incision in the vaginal wall, through the obturator membrane and out through the inner thigh. The trocar is then removed leaving the sling *in situ.*

The safety and efficacy of the inside-out TVT-O™ was investigated by Waltregny *et al.*, (56) whose prospective, observational trial found a subjective and objective cure rate of 91% for 253 women at 12 months' follow-up. Postoperative voiding symptoms were reported in <10% of patients. No bladder or urethral perforations occurred during the procedures, and no vaginal or urethral mesh erosions were noted after surgery. QOL, assessed using the Ditrovie self-questionnaire, was significantly better after surgery than at baseline (P <0.0001). Follow-up at 3 years revealed similar results. (57)

The inside-out and outside-in approaches to the transobturator midurethral sling have been compared in several meta-analyses. Novara *et al. (50)* reported an equal rate of objective success between the two approaches at 4 months in three trials comprising 280 patients who underwent transobturator mesh sling insertion (OR 1.96, 95% CI 0.84–4.53; P = 0.12). Latthe *et al.(58)* also found an equal rate of both subjective (OR 1.37, 95% CI 0.93–2.00; P >0.05) and objective success rates (OR 1.06, 95% CI 0.65–1.73; P >0.05). Bladder injury and voiding difficulties were less frequent with the inside-out technique than the outside-in technique (OR 0.17, 95% CI 0.005–0.05 and OR 0.49, 95% CI 0.24–1.04, respectively).

Moreover, multiple studies confirm that TVT-O is safe and effective in the long term. These studies include: Tommaselli GA, *Tension-free vaginal tape-obturator and tension-free vaginal tape-Secur for the treatment of stress urinary incontinence: a 5-year follow-up randomized study*. Eur J Obstet Gynecol Reprod Biol. 2015 Feb; 185:151-5; Tommaselli GA, *Medium-term and long-term outcomes following placement of midurethral slings for stress urinary incontinence: a systematic review and metaanalysis*. Int Urogynecol J. 2015 May 20; Athanasiou S, *Seven years of objective and subjective outcomes of transobturator (TVT-O) vaginal tape: why do tapes fail?* Int Urogynecol J. 2014 Feb; 25(2):219-25. Laurikainen E, *Five-year results of a randomized trial comparing retropubic and transobturator midurethral slings for stress incontinence*. Eur Urol. 2014 Jun;65(6):1109-14; Serati M, *TVT-O for the treatment of pure urodynamic stress incontinence: efficacy, adverse effects, and prognostic factors at 5-year follow-up*. Eur Urol. 2013 May; 63(5):872-8; Cheng D, *Tension-free vaginal tape-obturator in the treatment of stress urinary incontinence: a prospective study with five-year follow-up*. Eur J Obstet Gynecol Reprod Biol. 2012 Apr; 161(2):228-31; Liapis A, *Efficacy of inside-out transobturator vaginal tape (TVTO) at 4 years follow up*. Eur J Obstet Gynecol Reprod Biol. 2010 Feb; 148(2):199-201.

TVT OR THE TVT-O PROCEDURE

Novara *et al.* (50) found the retropubic approach was associated with a significantly higher rate of objective success than the transobturator technique (OR 0.8, 95% CI 0.65–0.99; P = 0.04). Subjective success rates were equivalent. The obturator approach resulted in fewer bladder and vaginal perforations (OR 2.5, 95% CI 1.75–3.57; P <0.0001) and fewer patients with storage lower urinary tract symptoms (OR 1.35, 95% CI 1.05–1.72; P = 0.02).

Ogah *et al.* (49) compared retropubic and obturator slings in a meta-analysis that included 24 trials. Subjective cure rates at 12 months were available for a total of 1,381 patients. No statistically significant difference was found between retropubic and transobturator slings, with patients in both groups reporting an 83% success rate (RR 1.00, 95% CI 0.96–1.05). Objective cure rates at 12 months for 2,434 patients were 88% and 84% in the retropubic and transobturator groups, respectively (RR 0.96, 95% CI 0.93–0.99).

Richter *et al.* (4) reported the outcomes of 597 women randomized to undergo either retropubic (n = 298) or transobturator (n = 299) midurethral sling insertion. Self-reported symptoms, urinary stress tests, pad tests and retreatment rates were assessed. Objective success rates (defined as a negative provocative stress test, a negative 24 h pad test and no retreatment for SUI) at 12 months were 80.8% in the retropubic group and 77.7% in the obturator group (3% difference, 95% CI 3.6–9.6). Statistical analysis demonstrated equivalence for both procedures in objective measures; however, retropubic slings performed slightly better subjectively (62.2% versus 55.8%; 6.4% difference, 95% CI 1.6–14.3). Intraoperative blood loss was greater in the retropubic group than the transobturator group (50 cc versus 25 cc; P <0.001), as was the operative time (30 min versus 25 min: P <0.001). Although these values were statistically significant, they are unlikely to be clinically significant. The rate of serious adverse events was 13.8% in the retropubic group and 6.4% in the transobturator group (P <0.03), with higher rates of UTI (P = 0.04), bladder perforation (5% versus 0%) and voiding dysfunction requiring surgical intervention (2.7% versus 0%; P = 0.004) reported by those who underwent retropubic sling insertion. Neurologic complications (new paresthesias or motor deficit at 6 weeks) were more common in the transobturator group (9.4% versus 4.0%; P = 0.01) as were vaginal perforations (4.3% versus 2.0%). No significant differences in *de novo* urge incontinence, patient satisfaction or QOL were reported between groups. Mesh complications (3.4%) were uncommon (16 exposures and 2 erosions) in the first 2-years. There were only 7 new mesh erosions (3 TVT™, and 4 transobturator slings) between year 2 and 5.

Overall, these data suggest that the retropubic approach offers a slight advantage over the transobturator approach in terms of objective cure rates. Each technique is associated with a different adverse effect profile; with the retropubic approach causing a higher rate of perioperative complications.

COMPLICATIONS OF THE TVT AND TVT-O PROCEDURES ARE MINIMAL

A 2015 Cochrane Review of the peer reviewed literature concluded that "midurethral sling operations are the most extensively researched surgical treatment for stress incontinence in women, have a good safety profile…. and are highly effective in the short and medium term… accruing evidence demonstrates their effectiveness in the long term." (59). The authors also conclude that midurethral slings have a "positive impact on improving quality of life of women with stress incontinence."

Ford (59) reported the following complication rates from registries for the retropubic midurethral sling: bladder perforation 2.7 – 3.9%, reoperation rates relating to tape insertion or postoperative voiding dysfunction 1.6% - 2.4%, urinary retention rate was 1.6%, pelvic hematoma 0.7% - 1.9%, infection rate was 0.7%, vaginal tape erosion/extrusion rate was 1.5%, groin pain occurred

in 0.4% of women. Similar rates were reported for transobturator slings: bladder perforation 0.4%, reoperation rates relating to tape insertion 0.8% - 2.2%, urinary retention 0.5%, pelvic hematoma 0.5%, infection rate 0.6%, vaginal tape erosion/extrusion rate was 0.4%, and groin pain occurred in 1.6% of women.

These rates are consistent with the FDA's analysis of complication rates from the MAUDE database showing around 2% mesh exposure, and the Medicines and Healthcare Products and Regulatory Agency (MHRA) in Europe publishing a low vaginal tape erosion rate between 1.1% to 2.5%. In their 2014 report, the MHRA concluded that there appeared to be no evidence that vaginal mesh implants for SUI are unsafe. Moreover, over 50% of the mesh exposures are managed expectantly as the patients are asymptomatic. Native tissue repairs with permanent or absorbable sutures can also result in suture exposures and erosions, which could require a re-operation or simple office excision of the exposed or eroded suture.

Post-operative chronic pain and dyspareunia are rare complications associated with both the retropubic and transobturator midurethral sling (60).

GROIN PAIN

Persistent pain in the groin or thigh is another troublesome complication of midurethral slings that occurs more commonly with the transobturator approach than retropubic surgery. Laurikainen *et al.*(61) reported that 16% of women randomized to undergo insertion of an inside-out transobturator sling experienced groin pain compared with only 1.5% of those in the TVT arm. Similarly, Wang and colleagues (62) reported pain in 8.2% of patients after TVT-Ocompared with only 2.6% of those who underwent TVT insertion. In meta-analyses, Long *et al.*(62) and Latthe *et al.*(58) confirmed that groin or thigh pain was reported more frequently after transobturator insertion than retropubic procedures.

However, groin or leg pain with TVT-O is usually transient and typically resolves in the post-operative period. The literature has shown that while TVT-O has a higher rate of groin pain than TVT in the immediate post-operative period, the groin pain rarely persists in the long-term. At 7.5 year follow-up, Athanasiou (63) found that no patients reported persistent groin pain at the longterm follow-up. Similarly, Serati (64) and colleagues found that 9.9% of patients complained of groin pain 24 hours after the TVT-O procedure, while 3.1% complained of groin pain at six month follow-up, 1% at one year follow-up, and at 5 years, no cases of groin pain remained.

Recent systematic reviews by Ford (59) and Tommaselli(65) evaluating the safety of retropubic and transobutrator midurethral slings concluded that 'midurethral sling operations have been the most extensively researched surgical treatment for stress urinary incontinence in women and have a good safety profile. Irrespective of the routes traversed, they are highly effective in the short and medium term and accruing evidence demonstrates their effectiveness in the long term." When comparing transobutator and retropubic approaches, the authors of the Cochrane Review found that there were no statistically significant differences in rates of overall perioperative

complications between the procedures. Overall, vaginal mesh exposures were not different for retropubic or transobturator midurethral slings (approximately 2%).

Rates of postoperative pain were low with both transobturator and retropubic midurethral slings (4.5%), and when pain was reported the 'occurrences were short lasting, with most resolving in the first 6-months'. Tommaselli found no differences in postoperative pain (OR 0.78) nor persistent voiding dysfunction (OR 1.23) between retropubic midurethral slings or transobturator midurethral slings. The authors concluded that the similar efficacy of retropubic and transobturator midurethral slings is "backed by a high safety profile, and by a limited number of complications which were seldom severe."

In summary, for women considering a retropubic or transobturator MUS, Schimpf et al (60) recommend either the TVT or the Transobturator TVT-O intervention as the objective and subjective cure are similar; the decision should be based on surgeon expertise accounting for adverse events.

Post-operative chronic pain and dyspareunia are rare complications associated with both the retropubic and transobturator midurethral sling (60). In a randomized trial of 565 women undergoing TVT or transobturator sling, only 2% of those undergoing TVT reported any pain beyond 6-weeks after surgery. Pelvic pain and dyspareunia are common conditions among the general population, even for women who haven't undergone pelvic surgery, and have also been reported in the medical literature for traditional procedures (66). TVT has been shown to improve sexual function. (67)

SOCIETY STATEMENTS ARE IN FAVOR OF THE TVT MESH

The American Urogynecologic Society (AUGS), American Urological Association (AUA) and National Institute of Health and Care Excellence (NICE) have all come out with position statements on SUI treatments. These organizations and others have concluded that the TVT mesh is safe. NICE also stated that devices should use type 1 macroporous polypropylene tape, for which the TVT is made.

AUGS (with over 1,700 members) and SUFU (with over 500 members) adopted a joint position statement in 2014 highlighting the following about the safety and efficacy of midurethral slings:

- Polypropylene material is safe and effective as a surgical implant. Polypropylene material has been used in most surgical specialties (including general surgery, cardiovascular surgery, transplant surgery, ophthalmology, otolaryngology, gynecology, and urology) for over five decades, in millions of patients in the US and the world (personal communication with manufacturers of polypropylene suture and mesh). As an isolated thread, polypropylene is a widely used and durable suture material employed in a broad range of sizes and applications. As a knitted material, polypropylene mesh is the consensus graft material for augmenting hernia repairs in a number of areas in the human body and has significantly and favorably impacted the field of hernia surgery. As a knitted implant for the surgical treatment of SUI, macroporous, monofilament, light weight polypropylene has demonstrated long term durability, safety, and efficacy up to 17 years. [51].

AUGS-SUFU MATERIAL SAFETY FAQs by Providers on Mid-urethral Slings for SUI
2014 Mar 12

Does the evidence indicate that mid-urethral slings are safe in the treatment of SUI?
The MUS is the most studied anti-incontinence procedure in medical history. Furthermore, it is likely that more individuals have undergone this surgical procedure for the treatment of SUI than any other.

What is the material used for mid-urethral slings and have studies shown the material to be safe?
Currently available mid-urethral slings are composed of macroporous, knitted, monofilament polypropylene, sometimes known as “Type I” meshes. As a suture material, polypropylene is widely used, durable and employed in a broad range of sizes and applications. Polypropylene material has been used in most surgical specialties (including general surgery, cardiovascular surgery, transplant surgery, ophthalmology, otolaryngology, gynecology, and urology) for over five decades, in millions of patients in the US and the world.

Does the MUS mesh made of polypropylene degrade over time?

Polypropylene is a stable and well-accepted biomaterial with a history of over five decades of use in mesh implants. In recent years, concerns regarding implanted polypropylene degradation have been raised as a result of very high-magnification images that show portions of some explanted synthetic meshes with "cracked" surfaces.[8] These surface changes were further hypothesized to lead to adverse clinical outcomes, though this is not supported by the extensive peer-reviewed literature related to polypropylene mesh repairs.

Is there scientific evidence that the mesh used in polypropylene mid-urethral slings causes cancer in humans?

Tumors related to the implantation of surgical grade polypropylene for mid-urethral slings in humans have never been reported. There is no compelling evidence supporting human malignant transformation related to polypropylene despite the millions of individuals implanted with various forms of this material spanning well over a half century world-wide. The possibility that biomaterial prosthetic devices could cause tumors or promote tumor growth has been the focus of extensive research by both clinicians and biomaterial researchers. It is known that tumor formation related to biomaterials in animals is largely dependent on the physical, not the chemical configuration of the implant, with smooth large surface areas (discs and thin sheets) being potentially carcinogenic, and irregular disrupted surfaces (e.g. those that contain pores as in meshes) lacking carcinogenicity.

Has there been an FDA recall of mid-urethral slings or the mesh material?

None of the FDA communications regarding mesh used in pelvic reconstructive surgery were related to a recall nor did they suggest that the material or implantation of mid-urethral slings were dangerous, or should be stopped.

I agree with all these various professional society statements as they are consistent not just with my clinical experience, but my extensive review of the medical literature.

GENESIS AND RATIONALE FOR THE TVT SECUR SYSTEM

In 2006, the third generation TVT-SECUR suburethral system was developed in order to allow for trocarless delivery of suburethral sling that would therefore eliminate or minimize the risks of passing trocars through either the retropubic space (TVT) or the transobturator and groin passage(TVT-O).

The main risks of the retropubic TVT passage are bladder injury and injury to the blood vessels. Some of these injuries especially to the blood vessels could be catastrophic.

The problem documented with the trans-obturator passage has classically been groin pain that is usually transient but could last a few weeks. Also, there is concern about voiding dysfunction.

Elimination of trocars could possibly help prevent these complications.

The other reason was that this procedure could now be performed entirely under local anesthesia and this could hasten recovery and eventually allow this procedure to be performed in an office-based setting. This would make the procedure more acceptable to women suffering from this condition and take away the deeply ingrained fears associated with "bladder suspensions".

The TVT secur suburethral sling is an 8 cm X 1.1 cm mesh sling. The challenge was how to adjust the sling tensioning while allowing for the 2 inserters to be present in the 1.5 cm vaginal insertion incision AND allow for the surgeon to maintain dexterity and ability to function in that tight space.

There was no longer going to be a pull through of the mesh from the groin or the abdomen and this would mean that for the disengagement of the mesh to happen, the inserters would have to be withdrawn from the same vaginal incision.

Also, what would be the optimal length of the sling that would conform to all pelves types and allow for anchoring especially to the obturator internus muscle.

The other goal of the TVT SECUR sling was to allow urethral support similar to the retropubic TVT sling known as the TVT-SECUR 'U" approach or similar to the transobturator TVT-O sling by anchoring to the obturator muscles known as the TVT SECUR 'H" Hammock approach.

DEVICE DESCRIPTION

The text that follows is, in part, from Ethicon documents describing the composition, concept, and pre-market testing of TVT Secur. Based on my experience and review of medical literature, I believe the statements that follow are accurate.

The sterile single patient TVT SECUR system consists of 6 components: 1) TVT secur implant, 2)unprotected inserter, 3)protected inserter, 4) finger bad, 5) protective cover and 6) the release wire

1- **The TVT SECUR* Implant** is one piece of blue (Phthalocyanine blue, Color index Number 74160) PROLENE* polypropylene mesh (tape) approximately 1.1 cm in width and 8.0 cm in length that is sandwiched at both ends with an absorbable fleece composite material ETHISORB that is made from polyglactin 910/polydioxanone (typically known as Vicryl) coated with polydioxanone (typically known as PDO used in PDS sutures) film . The Vicryl and PDS materials are undyed. Both materials are combined using a thermoplastic process and the resultant fleecy material is of sufficient pore size to allow continuing growth of cells and intrinsic body tissue. The absorbable ends stiffen the mesh to facilitate passage, aid in tactile insertion of mesh implant, and increase friction to assist in securing the mesh operatively.

Absorption of sandwiched fleece ends is essentially complete within approximately 90 days , the fleece layers are replaced as connective tissue grows into the mesh. Portions of the PDS yarn/film can be detected up to 180 days post-implantation.

Ethisorb has been used in other products like Ethicon Dura Patch and also in non-sterile environment as a dental packing following dental extractions for more than 10 years and there is extensive data about its safety as an implant for use in humans.

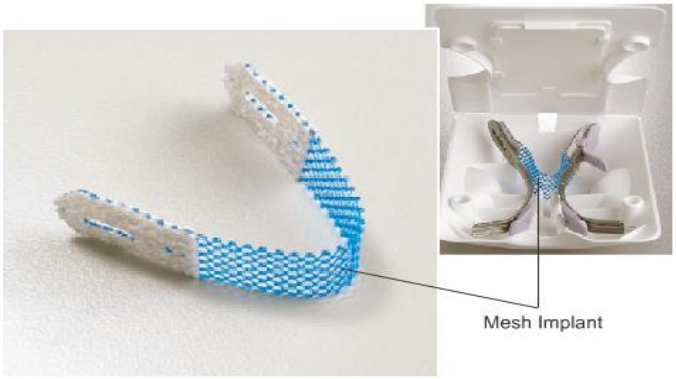
PROLENE polypropylene mesh is constructed of knitted filaments of extruded polypropylene strands identical in composition to that used in PROLENE* polypropylene non-absorbable surgical sutures. Prolene mesh is knitted by a process that interlinks each fiber junction and which provides for elasticity in both directions. This bidirectional elastic property allows adaptation to various stresses encountered in the body. The Prolene/polypropylene mesh utilized in TVT SECUR is identical in composition/ structure to the original mechanically cut mesh used in marketed TVT products; however it is laser cut to size similar to the TVT and TVT Obturator line extensions. Clinical differences between devices utilizing the laser cut versus mechanical cut Prolene/polypropylene mesh devices are not seen in the physiological range is equivalent to the mechanical cut mesh when tested

The polypropylene mesh utilized in TVT SECUR differs from the mesh used in the previous TVT products in that the mesh is laser cut rather than mechanically cut. Studies have demonstrated that the elongation of laser cut mesh is equivalent to the mechanical cut. Moreover, clinical studies have not shown any difference in clinical outcomes or any specific side -effects due to one or the other. There have been anecdotal reports from individual surgeons stating "their perception" without there being any published evidence of differences between the two different mesh cutting techniques.

In my opinion, based upon reasonable degree of medical certainty and also my extensive experience using both the mechanical and laser cut mesh systems, I have not seen any difference in outcomes or complications between the two.

The claims of the plaintiff's attorneys that the mechanical cut mesh frays when stretched, has never been substantiated in clinical practice and one should NEVER be subjecting the mesh to such excessive tensioning as seen in a lab setting. The physiologic range on tension exerted on the sling leads to no difference in stretch between the mechanical or laser cut mesh systems.

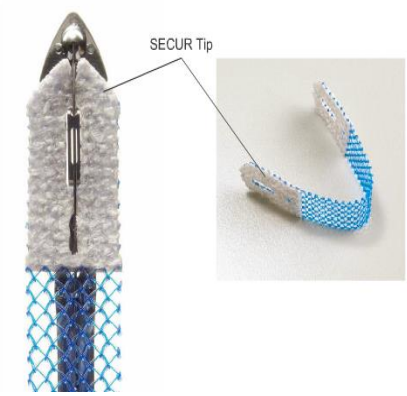
I have never seen fraying of any mesh system. I would state that based upon my knowledge of the literature and my own extensive experience using the TVT suburethral mesh systems, that if there is fraying noted then the surgeon is putting the mesh under tremendous tension, something that is not recommended.



INSERTERS

The Inserters (Fig.1, B & C) are two curved stainless steel instruments to which a standard needle driver/holder attaches as a stabilizer for controlled insertion.
The Inserters are provided pre-assembled with the Device and are designed to deliver and release the Device. The tip of one inserter is protected with a protective cover (Fig.) to avoid injury of the patient or the surgeon while the unprotected inserter is being used on the contralateral side. The unprotected inserter is always the first one to be inserted into the patient.
The protective cover is made from a radio opaque material to aid in ensuring it has not been left behind, in the event it cannot be located.

FINGER PADS
The finger pads (fig) have multiple functions, they protect the surgeon's fingers during insertion, they act as a saddle to help direct the device during placement and also Act as a retainer/stop for the release wire. The fingers pads are made from a radio opaque material to aid in ensuring it has not been left behind, in the event it cannot be located.



RELEASE WIRES
The release wire's primary function is to securely retain the implant to the inserter during insertion and adjustment of the implant. This is done by passing the wire through and over the implant in multiple locations as it also passes through the spring mechanism of the inserter body and into the tip locking mechanism. The second function of the release wire is to release the device (implant) from the inserters once they are correctly positioned.

Concept and Feasibility

Cadaver and study labs were done to see how the TVT-SECUR interacts with the host tissue. During this phase (for example) the following design questions were evaluated, some were confirmed and others were confirmed in the development phase:
To define the overall design and procedure the following were evaluated:

- Implant finger pitch, fingers or no fingers on implant, inserter radius, tip sharpness, inserter strength, procedural steps, impact of the inserter width vs the implant width, safety concerns, guide or no guide, handle or no handle, inserter strength and sharpness, length and width of the inserter, length and width of the implant, laser cut or mechanical cut mesh, sheath or no sheath?

To define the insertion device the following were evaluated:

- Numerous concepts were designed and built, not all were used, or successful, however they helped to move our understanding closer to what is now the final design.

Development of inserter and implant

The concept and development work of the inserter was narrowed down to the spring clip concept, which was able to securely hold the implant during insertion and consistently release the implant once positioned. This was a design challenge, when combined with not obstructing the urethra, not obstructing the surgeon's vision, ensuring safety to organs, patient and surgeon, ensuring that the final position of implant will not be altered during release and making one device that could be used universally in either the "U" or "hammock" approaches. This was achieved and documented through numerous labs and studies, in which various manufacturing challenges were refined. The concept and development work of the implant was paralleled with the many labs during this project, many of which contained more than one specimen. Primarily, the main focus was to define an implant length that was suitable for both the "U" or "hammock" approaches. Implant lengths as long as 14cm and as short as 5cm were evaluated. The final universal size selected was 8cm, with each end of the mesh covered by a 2cm sandwich of absorbable material leaving 4cm of exposed mesh to sit under the urethra, as does the currently marketed TVT device. A universal length is possible since the human pelvic structure does not vary much between individuals and patient weight does not have an impact on the pelvic region. This has been shown by Prof. J. De Leval. Besides the implant length, the fixation means, end shapes, or finger sizes were evaluated either in a cadaver or sheep study model. The 0.5 pitch design was chosen and then modified to have every other 0.5 pitch removed. This design allowed for maximum holding power, best surgeon perceived adjustability during positioning and was favorable from a design for manufacturing perspective. In most labs, the holding force of the implant was either measured or evaluated; some labs evaluated the implant's ability to remain as placed after release by either a tactile assessment or use of fluid measurement equipment.

Once the inserter and implant design were frozen, numerous cadaver labs were conducted to ensure that they worked as a system. The manufacturing processes were then confirmed to be able to produce the final designs. Additionally, the surgical procedure was also refined and written as draft instructions for use (IFU) from these study labs. This draft IFU was then reviewed and used subsequent labs with current TVT device experts, Anatomists, Gynecare's Medical Director and approved by out two key opinion leaders surgeons who were instrumental in the device design.

<u>Expert opinion from TVT Obturator inventor and confirmation of the IFU (using the final design)</u>

One lab was conducted as per the IFU and documented with Professor J. De Leval from Belgium, inventor of Gynecare's TVT Obturator device and his anatomist Dr. P. Bonnet to gain their expert opinions regarding the new TVT SECUR design and anatomical perspective. Both the "U" and "Hammock" TVT SECUR placements were evaluated and dissections of both were done. This lab was successful and the new device was said to be unique, it functioned as intended, it was used successfully and implant placements were as expected. Comments from the lab regarding further clarity to improve patient safety were included into the next IFU revision.

<u>Surgeon input, finalization of the IFU (Using the final design)</u>

Four cadaver labs were conducted as per the IFU (some labs used two specimens) and documented.

One lab was conducted with Gynecare's Medical Director Dr. C. Owens to confirm that design of the proposed device could indeed be suited as a universal device, to confirm final device placement, to evaluate its safety, and ability to be placed as described in the proposed IFU package insert. This lab was successful, the device was used successfully, the device performed as expected, and placements were as expected. Minor changes to the IFU were made for clarity. There additional labs were conducted using two surgeons; Dr. R. Rodgers did two and Dr. C. Haynes did the other. These labs all were carried out at different times but for a similar purpose, which was to confirm that the device worked as expected, and the proposed IFU contained appropriate information to perform the procedure. Dr. R. Rodgers and Dr. C. Haynes did not have previous exposure to the procedure.

In summary, these labs were conducted as expected and appropriate learning (clarifications) from each were incorporated into the final package insert (IFU).

SHEEP AND HUMAN CADAVER STUDIES

The TVT SECUR system is designed to anchor into either the urogenital diaphragm or the obturator internus muscle. Unlike the predecessor TVT and the TVT-O slings, the TVT-SECUR does not exit the muscles of the abdominal wall nor the obturator/adductor muscle complex and hence its fixation forces needed to be determined to see if they withstood the physiological range of tension and also whether the pull-put forces were as good as the TVT sling.

Human and sheep cadaver studies were conducted in order to determine this.

An initial sheep study was performed in 2004. The sheep model was chosen as it offered the most comparable system to the human female regarding tissue properties and size of anatomy[78]. Eight female sheep (mix of Texel, Finewool, Shopshire) were used in this study. The use of two sheep at each time point allowed evaluating pullout force at four time points (1, 2, 4, and 12 weeks). Conceptually, the fixation process of TVT SECUR should be divided into three phases: (1) the initial phase of mechanical fixation of Ethisorb ends through friction with the tissue; (2) the midterm fixation through in-growth of tissue into the polypropylene mesh area; and (3) the final fixation through strong bonding of the end parts of the mesh to the surrounding tissue. The hypothesis for this current trial was that a decrease in the fixation force (friction) over time due to the absorption of Ethisorb parts of TVTx would have been compensated by the increase in fixation force due to the in growth of tissue into the whole mesh.

The objectives of the study were to assess whether the fixation force of an implanted TVT SECUR device (called TVT x at the time of the study) would measure at least 5 Newtons (considered an adequate force) at time "zero" and would remain above 5 Newtons through the duration of the study. Five Newtons was originally chosen to align with the approximate force needed to stretch the TVT mesh to a length 50% greater than its starting point. This load is well beyond the working loads exerted by the body, but at the time of this study physiological values were not known.

The mean pullout forces of TVTx were 2,329±742 g in week 1, 3,658±1,772 g in week 2, 5,613±1,819 g in week 4, and 6,509±1,169 g in week 12 ($p<0.001$). Pullout forces during the whole trial were never less than 600 g. The pullout forces of TVTx proved to be sufficient immediately at 1, 2, 4, and 12 weeks after implantation into the sheep's retropubic area. The pullout forces increased during the study considerably from week 1 until week 12. Immediate pullout forces were in the range of the standard retropubic TVT.

So, the primary objective (pullout force of TVTx at week 1, 2, 4, and 12 is greater than 5 N) was fulfilled. The secondary objective of the TVTx fixation force being as high as the initial fixation force of standard TVT was proved as well.

Additional information obtained from the study results were that there were no signs of infection, or any other side effects from the mesh and that histologic examination of the tissue around the implant showed good in - growth of the surrounding tissue into the mesh with no abnormalities.

Confirmation of Fixation Force of TVT SECUR in a Sheep Cadaver Model Development – Study 2

The prototype TVT x design used in the 3-month live sheep study had "fingered: absorbable fleece ends and were implanted using standard forceps. A design change eliminated these "fingers" to better achieve the desired placement under the urethra and improve tactile feel during placement. The "finger-less" implant shape of the TVT SECUR implants used in sheep cadaver (pre-clinical study 2) were consistent with the final product specifications and were straight in design with the edge roughness characteristics. Implants were laser cut utilizing the final manufacturing process. Additionally, the TVT SECUR device was attached, implanted and released to this study using the final inserter instrument designed to cut a precise tissue opening.

Also the prototype TVT-x was subjected to a load of 5 newtons which is well beyond the working loads exerted by the body, but at the time of the initial sheep study physiological values were not known. Since that time, the Lin study showed that the body exerted forces on the sling that were in the 50 gram range. Ethicon's internal testing evaluated the GYNECARE TVT mesh to establish the "point" in which plastic (or permanent) deformation occurs. This "point" which called the "Physiological value" is equal to the Yield Point of TVT mesh +2 Standard Deviations; this equates to 130 grams +2*17 = 164 grams. The 164 gram threshold was therefore used in later animal and human studies conducted by Ethicon. Additionally, it was expected that the fixation forces of new implant would be at least similar to the initial fixation force of a traditional TVT mesh (pulled out immediately after insertion).

In the secondary sheep study, the mean pullout force for the TVT SECUR mesh following implantation was 1095.1 g and the minimum pullout force across all 10 animal models of 567g was 3.5 times higher than the target value of 164 g. Placement of the TVT SECUR mesh transvaginally into the connective tissue of the urogenital diaphragm or through the obturator

internus muscle resulted in pullout forces exceeding 164 g for all implants in a human cadaver model (mean values of 788.3 and 1154.3 g, respectively). The pullout force following initial placement of the TVT SECUR mesh did not differ significantly from that for traditional TVT or TVT Obturator implants in the same model.

Evaluation of Fixation Force for TVT SECUR Implanted in Human Cadaver Tissue (Study 3)

The TVT SECUR inserter with attached mesh implant was inserted through a vaginal incision, lateral to the urethra in each female cadaver pelvis. For the "U" placement it was in contact with the connective tissue of the urogenital diaphragm of the pubic bone. For "H" placement it was in contact with the inferior edge of the pubic ramus and located in the internus muscle. The laminated fleece sandwiched ends of the TVT SECUR were inserted to an approximate depth of 1 to 2 cm and the release wire was removed.

In each cadaver, a second implantation of the traditional TVT/TVT Obturator or TVT SECUR devices was performed adjacent to the first insertion to determine the impact of reinsertion.

Human cadaver studies demonstrated that on the initial pass of polypropylene mesh transvaginally into the connective tissue of the urogenital diaphragm (and not continuing through the retropubic space and exiting the skin) resulted in adequate fixation of the mesh. The pullout forces were similar to that of conventional GYNECARE TVT.

Similarly, the pullout force of the tape passed only through the obturator internus muscle (and not through the muscles and skin of the thigh) were similar to the pullout forces of traditional transobturator placed meshes.

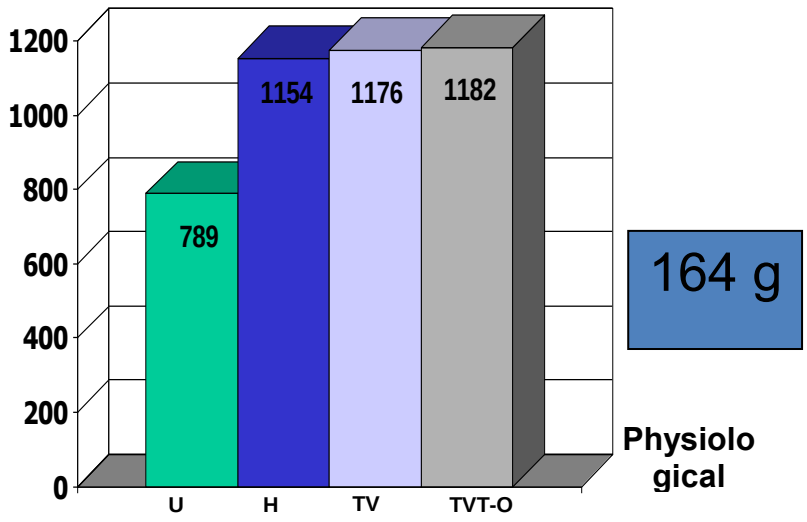
Effects of Reinsertion of TVT SECUR Device regarding Functionality and Integrity (Study 4)

Finally, a study was conducted to assess and confirm the device's ability to remain intact during multiple insertions in dense tissue and then be able to deploy the implant as designed. In this study ten out of ten implants were inserted 3 times each (30 total insertions). After the third insertion the release wire was pulled, the inserter was removed and the pullout force of the implant was measured. All criteria for this test were met. This was a very stringent test that challenged not only the integrity of the connection end of the implant to resist damage, but also the devices ability to not deform and deploy as designed. Initial holding ability was also challenged by stimulating a doublewide incision to stimulate a worst-case condition caused by reinsertion.

SUMMARY

TVT SECUR design has shown that when properly placed as intended, it can deliver the required initial security to hold the mesh until permanent tissue in-growth occurs. The single-sided pullout testing done in this study represents a worse case condition since in actual clinical use, both ends of the mesh would be imbedded into tissue and provide support.

The human cadaver studies demonstrate that placement of the Prolene polypropylene mesh transvaginally into the connective tissue of the urogenital diaphragm or through the obturator membrane resulted in single-sided pullout forces for all TVT SECUR implants that exceeded 164 g regardless of the "U" or "H" insertion location. Additionally, the TVT SECUR device remained intact up to 3 insertions in dense tissue of the rectus femoris muscle and exceeded the physiological value of 164 g by at least a factor of 2 at pullout. This test ascertained the integrity of the design, implant connection and deployment after multiple insertions.



Evaluation of the Pullout Force of GYNECARE TVT SECUR* System implanted into the urogential diaphragm and obturator membrane of a human cadave

Gynecare TVT SECUR System

It is my opinion based on the company documents I've reviewed—of which the content of many are found in the above pages--my review of the medical literature and my personal involvement in the early years of TVT Secur that Ethicon conducted appropriate and adequate pre-market testing of TVT to ensure its safety and efficacy before being commercially launched.

For the same reasons, I agree with the following biocompatibility assessment from Ethicon regarding TVT Secur:

BIOCOMPATIBILITY AND LACK OF CARCINOGENICITY OF TVT SECUR

The two Surgical steel (SS) inserters and SS release wires are made of type 304 stainless steel, which is a common material for medical devices and surgical instruments with long history of safe clinical use. The polypropylene finger pads and protective cap are made of radiopaque, violet polypropylene, which is also a common material for medical devices with long history of safe clinical use. These components of the device will have no anticipated patient contact. Therefore no biocompatibility tests according to FDA G-95 Memorandum on the ISO 10993-1 guidelines had to be performed. However in case of inadvertent, transient patient contact and to confirm that the manufacturing process does not change the biocompatibility of these components, GLP biocompatibility studies were conducted on injection molded finger pads including cytotoxicity elution test (LPT report no. 19282/05) and intracutaneous reactivity (LPT report no. 19284/05). These studies indicated that polypropylene finger pads were non-cytotoxic and without adverse intracutaneous reaction.

The TVT SECUR device is similar to the base TVT device in that it uses the same PROLENE mesh construction and material, is placed under the mid-urethra. It differs from the base TVT device in that it is shorter than original TVT and includes two layers of polyglactin 910/polydioxanone fleece material coated with polydiozanone film sandwiched onto the PROLENE mesh on both ends on top and bottom with same synthetic raw material composition as Codman ETHISORB Durapatch. Codman ETHISORB Durapatch is a composite of a fleece of undyed polyglactin 910 and polydioxanone filaments, and a film of polydioxanone dyed with D&C violet No. 2. Polyglactin 910 is used to manufacture VICRYL (polyglactin 910) suture. Both of these synthetic absorbable sutures are well-characterized and biocompatible and have a long history of safe chemical use.

As indicated in the FDA G-95 Memorandum on the ISO 10993-1 guidelines entitled "biological Evaluation of Medical devices-Evaluation and Testing", PROLENE mesh and polyglactin 910/polydiozanone fleece material coated with polydioxanone film are categorized as an implant device having permanent contact with tissue. As such, and in accordance with the FDA guidance document entitled "Guidance for the preparation of a Premarket Notification Application for Surgical Mesh", a number of biocompatibility tests including cytotoxicity, sensitization, intracutaneous reactivity, acute systemic toxicity, material-mediated pyrogenicity, subchronic toxicity, chronic toxicity, genotoxicity, implantation, and carcinogenicity must be considered.

The long and extensive history of safe clinical use of polypropylene, specifically PROLENE mesh and PROLENE suture and Codman ETHISORB Durapatch which has 510 (k) clearance, demonstrates the biocompatibility of these materials.

It is considered that the extensive clinical experience with polypropylene precludes the need to conduct sensitization, acute systemic toxicity, and subchronic toxicity studies. The chronic systemic toxicity and carcinogenicity potential of polypropylene was evaluated using natural and blue PROLENE suture in the rat and dog indicating that this material was well-tolerated and non-carcinogenic (NDA 16-374; Vol. 1.1). This negative carcinogenicity result and long-term clinical experience preclude the need to conduct genotoxicity testing.

A number of intramuscular and ophthalmic implantation studies have been conducted for PROLENE sutures in the rat, dog, and rabbit for the original NDA as well as more recently where this material was used as the control article (Intramuscular Tissue Reaction-PSE 97-0162, Ophthalmic Tissue Reaction-PSE 97-0218, and Dura mater Tissue Reaction-PSE 98-0021). The results indicated that this "gold standard" material was well tolerated and without adverse effects. In addition, a 28-day intramuscular tissue reaction study was conducted in rats where PROLENE mesh was used as the control article (PSE 97-0197). The results indicated that the tissue reaction was generally mild, and the presence of the mesh did not impair the healing response. Most recently, a 18/2-day intramuscular tissue reaction study was conducted in rates where PROLENE mesh was again used to control article (PSE 99-0115). The results indicated that the tissue reaction was characterized by generally minimal to mild chronic inflammation that gradually decreased in intensity over the 182 day study.

A six-month intra-cranial dura tissue reaction GLP study in rabbits was conducted with Codman ETHISORB Durapatch (PSE 97-0069). The results indicated that this absorbable fleece composite was well tolerated and without adverse effects.

A peri-vaginal implantation Non-GLP study in sheep pelvic tissue (ETHICON GmbH SO 04/2-2-1) has been conducted on representative Gynecare TVT SECUR implants over 12 weeks. The results indicated that this PROLENE mesh and polyglactin 910/polydiozanone fleece material coated with polydiozanone film was well tolerated and without adverse effects. The polyglactin 910/polydioxanone fleece material coated with polydiozanone film of the implants was essentially absorbed between 4 and 12 weeks.

To confirm that the manufacturing process does not change the biocompatibility of the components, further GLP biocompatibility studies were conducted on final representative product including cytotoxicity elution test (LPT report no. 19281/05) intracutaneous reactivity (LPT report no. 19283/05) and material-mediated pyrogenicity (LPT report no. 19285/05). These studies indicated that PROLENE mesh and polyglactin 910/polydiozanone fleece material coated with polydioxanone film were non-cytotoxic, without adverse intracutaneous reaction and non-pyrogenic.

In summary, the preclinical biocompatibility study results and the extensive clinical experience with polypropylene as used in PROLENE mesh and PROLENE suture and polyglactin 910/polydiozanone fleece material coated with polydiozanone film as used in Codman ETHISORB Durapatch demonstrated that these base materials are intrinsically safe and without significant adverse effects. Since these materials are the basic components of GYNECARE TVT SECUR implant, similar biocompatibility can be expected. Further preclinical studies with

GYNECARE TVT SECUR implant, particularly the sheep peri-vaginal implantation study to evaluate a representative product have also demonstrated the biocompatibility of this device.

When considering the biocompatibility of TVT Secur, it is important to remember that the mesh in TVT Secur is identical in composition and construction to the mesh in TVT and TVT-O. At the time of TVT Secur's launch, Ethicon had almost a decade of biocompatibility data from the medical literature reflecting the safety of the mesh in TVT and TVT-O upon which they were able to rely when assessing the biocompatibility of TVT Secur.

The following detailed procedural steps were provided by Ethicon to ensure proper conformance with the IFU. I was personally involved in Ethicon's efforts to ensure its communications to doctors was helpful, accurate, and sufficient to appropriately respond to the results some surgeons were seeing after improperly placing the device.

Procedural Steps: TVT SECUR System

- PATIENT POSITIONING
  Ensure a 90 degree position before draping

- VAGINAL DISSECTION
  - Vaginal: 1.5 cm sagittal incision after infiltration with local anesthetic
  - Sharp dissection of the vaginal epithelium ensuring that full thickness dissection is performed
  - Creation of the "landing pad": Undermining the vaginal incision at 12 and 6 o'clock position so that the TVT SECUR mesh lays flat under the mid urethra and is not curled.

- PARAURETHRAL DISSECTION
  - Appropriate infiltration of local anesthetic under the paraurethral vaginal epithelium until the epithelium balloons downwards. This would minimize the risk of laceration of the lateral vaginal epithelium especially when the inserter is passed towards the obturator internus muscle in the 'H' Hammock technique.
  - The lateral vaginal dissection should be as wide as the initial incision so that the inserter does not drag the epithelium and the paraurethral tissue.
  - Dissection must be in the same angle as the planned insertion toward lower edge of pubic bone for the U technique and towards 3 or 9 O'clock position for the H Hammock technique.

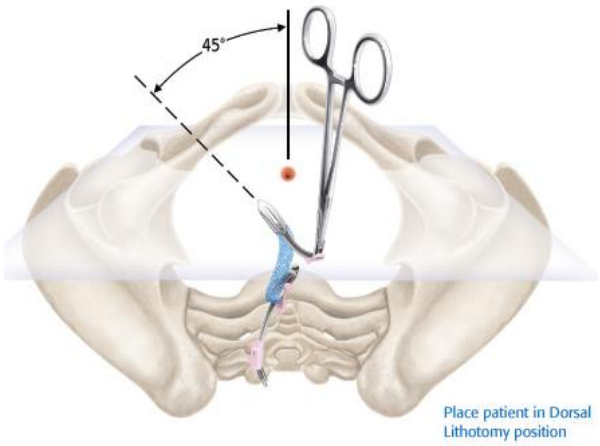
- CONNECTION OF NEEDLE DRIVER
  - Ensure needle driver is connected correctly – square up on the inserter in the channel groove

- PLACEMENT OF DEVICE
  - Target Tissue:
    Connective tissue of urogenital diaphragm at point of attachment to pubic bone for the U technique
    Obturator internus muscle for the H technique

'U' TECHNIQUE

POSITIONING OF DEVICE

- The bladder should be deflected to the contralateral side using the catheter guide.
- Rotate needle driver 45 degrees from the sagittal midline (vertical plane), to aim the entire device towards the ipsilateral shoulder
- Lift needle driver upright, so needle holder is in line with the vertical plane.

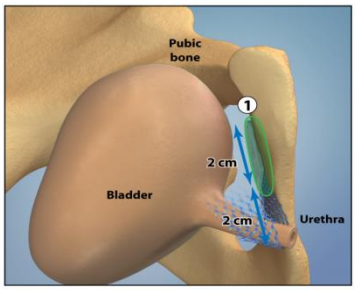


INSERTION OF DEVICE: FIRST INSERTION

- The needle driver is almost straight
- The index finger may be placed in the vagina in order to appreciate the landmarks during insertion
- The thumb is placed on the finger pad and it applies gentle pressure
- Advance the inserter straight in and contact the lower edge of pubic bone
- Once the pubic bone is reached, while maintaining constant contact of the tip of device with the back of pubic bone, drop the needle holder to a horizontal position
- **STOP** when device is firmly in connective tissue and has reached the posterior aspect of the pubic bone (-2 cm)
- Do not change the angle from the initial 45 degrees

Correct Placement

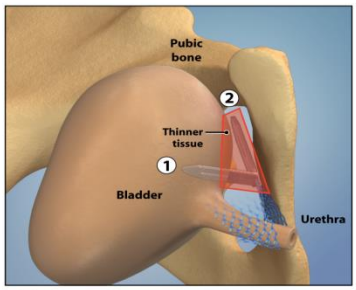
Close contact with pubic bone



① Correct final placement in close contact with lower edge of the pubic bone and in the dense connective tissue of the urogenital diaphragm.

Incorrect Placement

No contact with pubic bone



① After contact with bone, the handle was not tipped downward and not kept in close contact with the bone.
② The handle was tipped downward, but inserter did not keep close contact with the bone.

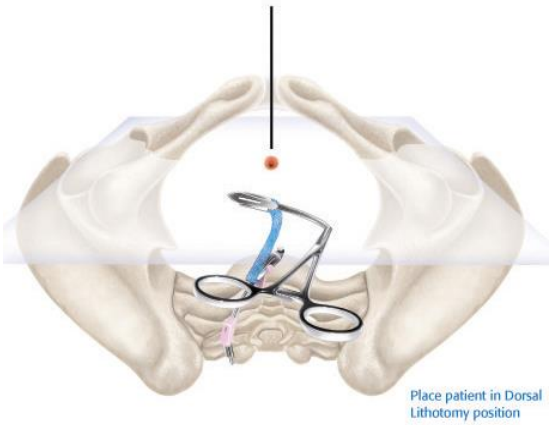
INSERTION OF DEVICE: SECOND INSERTER

- Disconnect the needle driver from the first inserter
- On second insertion, connect needle driver to the second inserter before taking protective cover off
  NOTE: Ensure the mesh is not twisted under the mid urethra prior to insertion on the second side
- Upon 2nd insertion, repeat above steps of positioning and insertion, while maintaining hand position
- Adjust the inserters as needed to achieve good mesh placement against urethra

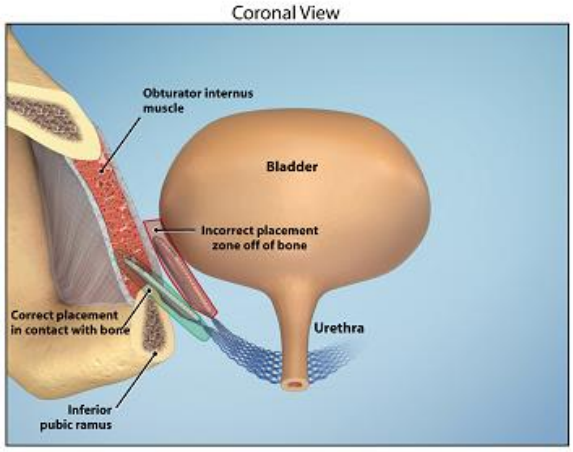
'H" HAMMOCK" TECHNIQUE steps:

- TARGET TISSUE: obturator internus muscle at the point it connects to the ischiopubic ramus

- Positioning of the device
  1. Device and needle driver must be parallel to the floor.
  2. Rotate the inserter tip at an angle of 45° from patient's midline, towards the ischiopubic ramus, while keeping the needle driver and device parallel to the floor



- Insertion of device: first inserter
    1. Ensure that the needle holder is parallel to the floor and angled at 3 O'clock position on the patient's left side
    2. Palpate obturator internus muscle with the index finger as the thumb is positioned on the finger pad
    3. make sure that the inserter clears the ischiopubic ramus
    4. Push device straight into obturator internus muscle while hugging the bone and ensuring the device is flat against the bone
    5. STOP when device is firmly in the obturator internus muscle.



- Insertion of device: second inserter
    1. Disconnect the needle driver from the inserter
    2. On second insertion, connect needle driver to the second inserter before taking protective cover off.

        NOTE: Ensure the mesh is not twisted under the mid-urethra prior to insertion on the second side
    3. Upon 2nd insertion, repeat steps 4 , while maintaining proper hand position

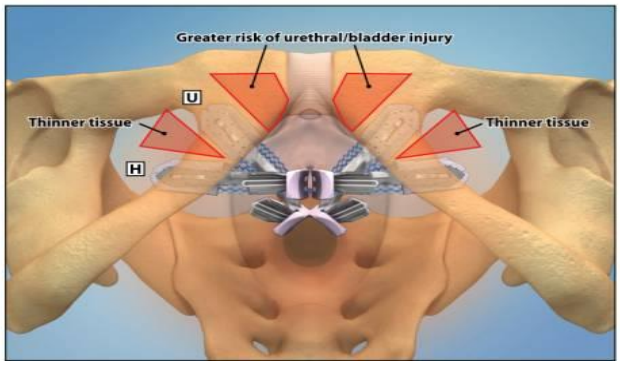
TENSIONING

- Make **FINAL** adjustment if needed by reconnecting the driver to the inserter. Establish proper hand position and advance or retract either inserter.
- Assessment should be performed **BEFORE** the release wire is pulled
  The tensioning protocol differs from surgeon to surgeon. Some would do a provocative cough test , some would perform the Credé maneuver while others would just look at appropriate tensioning under the urethra by visual inspection.
- Cystoscopy is required to confirm bladder integrity at the discretion of the surgeon for the hammock approach.
- Adjustment should be made by moving the inserters and not by pulling on the mesh

RELEASE OF INSERTERS

- This SHOULD ONLY BE DONE when one is certain of the sling tension as this should ideally not be adjusted once the inserter wire has been pulled back
- Release one inserter from the device by FULLY pulling back the release wire with the needle driver until ot comes to a STOP position while stabilizing the Inserter
- Use a **slight twist** with your hand to gently remove the inserter **without folding** it from the incision after the release wire hits "stop"
- A spacer or 10 mm malleable retractor could be used to hold the sling in place while the inserter is gently removed
- Brisk movements should be avoided as it could loosen the sling.
- Ensure **FINAL** sling position after removal of the 1st inserter. Adjust if needed on the opposite side. Then repeat removal of 2nd inserter.
- In some cases the inserter may be advanced a few mm in order to account for the slight loss of tensioning that may happen when the inserter is removed.
- Close the vaginal incision.

The Correct Placement of GYNECARE TVT SECUR "U" and "Hammock"



Since product releases in 2006, there have been no design changes in packaging material or IFU. The expiry dating (shelf life) or Gynecare TVT Secur devices have been changed from 2 years to 5 years.

The manufacturing equipment, process and drawings have been changed as follows:

- The knitted machine "Pfaff" was replaced by the new "STOLL" knitting machine in March, 2008. This change was initiated due to the discontinuation of the existing knitting equipment by the manufacturer.
- The process for grinding of the Release Wire Tip was hanged in January, 2009. This process change was made to improve life of production tooling. It did not change the specification or function of the Release Wire Tip itself. As such, it did not require drawing modifications.

The changes are invisible to the end user and have no impact to clinical usage of device.

INDICATIONS, CONTRAINDICATIONS AND WARNINGS

The Gynecare TVT Secur System is intended for use in women as a suburethral sling for the treatment of stress urinary incontinence (SUI) resulting from urethral hypermobility and/or intrinsic sphincter deficiency. This Device may be placed in either a "U" or "Hammock" position under the mid-urethra. Placement orientation is per the surgeon's preference.

The Gynecare TVT Secur System has been designed such that the procedure can be started on either the patient's left or right side.

Animal studies show that implantation of Prolene mesh and the absorbable fleece sandwich material made from Vicryl and PDS yarn elicit a minimal inflammatory reaction in tissues, which is transient and is followed by the deposition of a thin fibrous layer of tissue, that can grow through the interstices of the mesh system as the fleece portion is being absorbed, thus incorporating the mesh into adjacent tissues. The Prolene material is not absorbed, nor is it subject to degradation or weakening by the action of tissue enzymes.

<u>Contraindications</u>

As with any suspension surgery, this procedure should not be performed in pregnant patients. Additionally, because the Prolene polypropylene mesh will not stretch significantly, it should not be performed in patients with future growth potential including women with plans for future pregnancy.

<u>Warnings and Precautions</u>

- Do not use Gynecare TVT Secur System for patients who are not on anticoagulation therapy.
- Do not use Gynecare TVT Secur System for patients who have a urinary tract infection
- Users should be familiar with surgical technique for urethral suspensions and should be adequately trained in the Gynecare TVT Secur System before using.
- Users should be familiar with surgical technique for urethral suspensions and should be adequately trained in the Gynecare TVT Secur System before using.
- The Gynecare TVT Secur System should be used with care to minimize the chance of damage to large vessels, nerves, bladder and bowel. It is important to pay attention to the specific patient's anatomy while inserting the Device.
- Bleeding may occur postoperatively. Observe for any symptoms or signs before releasing the patient from hospital.
- For the "U" Position, a cystoscopy is required with a cystoscope that will provide full visualization of the entire bladder and urethra to assure no inadvertent penetration of the Inserter or device. If the Inserter or Device has penetrated any portion of the lower urinary tract, it must be removed and the patient evaluated.
- For the **"Hammock" position**, although bladder injury is unlikely to occur with this technique, cystoscopy may be performed at the discretion of the surgeon.
- Ensure that the tape is placed with no tension under the mid urethra.
- Acceptable surgical practice should be followed for the Gynecare TVT Secur System as well as for the management of contaminated or infected wounds.
- Do not perform this procedure if you think the surgical site may be infected or contaminated. If the Device is used in contaminated areas it must only be with the understanding that the subsequent infection may require its removal.
- Since no clinical information is available about pregnancy following suburethral sling procedure with the Gynecare TVT Secur System, the patient should be counseled that future pregnancies may negate the effects of the surgical procedure and the patient may again become incontinent.
- Since no clinical information is available about vaginal delivery following a suburethral sling procedure with the Gynecare TVT Secur System, in case of pregnancy, delivery via cesarean section should be considered.
- Postoperatively, the patient should be advised to refrain from heavy lifting and/or exercise (e.g., cycling, jogging) for at least three to four weeks and to refrain from intercourse for one month. The patient can usually return to other normal activity after one or two weeks.
- The patient should be instructed to contact the surgeon immediately if dysuria, bleeding or other problems occur.
- As with other incontinence procedures, de novo detrusor instability may occur following a suburethral sling procedure utilizing the Gynecare TVT Secur System. To minimize this risk, make sure to place the tape as described above.

- Do not affix the Prolene mesh with any staples, clips or clamps as mechanical damage to the mesh may occur.
- Do not re-sterilize the Device or the system's components. Discard opened, unused Devices.
- Prophylactic antibiotics can be administered according to the surgeon's usual practice.

Adverse Reactions

- Punctures or lacerations or injury to vessels, nerves, bladder, urethra or bowel may occur during instrument passage and may require surgical repair.
- Transitory local irritation at the wound site and a transitory foreign body response may occur. This response could result in extrusion, erosion, fistula formation or inflammation.
- As with all foreign bodies and surgical implants, Prolene mesh and absorbable materials may potentiate or exacerbate an existing infection.
- Over-correction, i.e., too much tension applied to the tape, may cause temporary or permanent lower urinary tract obstruction.
- Under correction or incorrect placement may result in incomplete or no relief from urinary incontinence.

CLINICAL STUDIES ON TVT SECUR

This review will summarize these, as follows:

- Observed safety and efficacy
- Sling positioning experience relative to "Hammock" and "U" position
- Observed cure rates
- Comparative performance relative to classic TVT and TVT-O tapes
- Observed complications and complication rates

I have reviewed and considered all the studies outlined below. These studies reveal that TVT Secur has been well studied and, despite some studies showing relatively lower efficacy rates (which I've also reviewed and understand are the basis, in part for the opinions of plaintiffs' experts), it's overall safety profile is that of a safe and effective product—especially when placed in strict accordance with the IFU.

Tommaselli, et al in their 2010 article reported on 84 patients with stress urinary incontinence (SUI) selected to undergo TVT-O or TVT-Secur. These researchers found no differences in

terms of cure rate between two groups (81.6% vs 83.8%) and the complication rate in the TVT-Secur group was lower (81.8%) than in the TVT-O group (15.8%), but not significant. Additionally, both techniques were judged to be effective and safe, with a low incidence of complication.

Oliveira, et al in their 2009 article reported on short-term surgical complications and results with the TVT Secur involving 107 patients. The operative duration was 12 min; the mean pain score was 2.3 and only one patient had transient voiding difficulties. After a mean follow up of 15 months, 71% of the patients were dry and 14% improved. The KHQ scores decreased significantly for most sub scores. de novo urgency was noted in six patients (5.6%) and vaginal erosion in one patient. The authors determined that TVT Secur is a simple and safe treatment.

I reported the finding for 141 consecutive patients treated with TVT-SECUR over a 15 month period. There were no intraoperative complications. Immediate postoperative voiding function returned in all but one patient; none required sling release. Most patients (90%) reported no pain on a verbal pain scale. On follow up, 117 patients reported no SUI symptoms, 16 reported mild symptoms and eight required additional treatment. The average MESA "stress" subscore improved 79%. Eighty-five percent (85%) felt "satisfied" with the procedure. The authors concluded that TVT-SECUR is a safe and effective treatment for SUI.

While many authors conclude the TVT Secur is safe and effective, several have indicated that there is a "learning curve" that should be taken into account. It is logical to hypothesize the effect of a "learning curve" for a new procedure. The following studies suggest the learning curve may or may not be apparent in both perioperative and postoperative findings. Too few studies have looked at this question, to this point in time, to be able to provide a definitive position on the "learning curve".

Martan, et al evaluated their first experience with the TVT SECUR mini sling involving 85 patients The efficacy was evaluated perioperatively and 3 month (+/- 1 week) after operation—subjectively by cough test and subjectively by the questionnaires Pelvic Organ Prolapse/Urinary Incontinence Sexual Dysfunction Questionnaire and the International Consultation on Incontinence Questionnaire Short Form. These authors observed a higher proportion of vaginal wall erosion (7/85) and de novo urgency (5/85) in the learning period group with respect to the routine period group. In their estimation the learning curve has to be taken in account with respect to postoperative complications.

Neuman, et al in their 2008 article reported on a prospective, observational and consecutive patient series in which perioperative and 12-month postoperative data were prospectively collected for the first 50 patients against the next consecutive 50 patients in a private hospital setting. Follow up at the end of 12 months postoperatively was completed with 44 (88.0%) of the first patient group and 46 (92%) of the second patient group. In all, 39 (88.6%) and 43 (93.5%) of the interviewed patients of the first and second groups, respectively, reported objective urinary

continence. The device was associated with early safety and efficacy problems. These included: the objective therapeutic failure rate for procedure among the first 50 patients was 20.0% (10 patients); 4 (8.0%) patients in the first group had vaginal wall penetration with the inserters, requiring withdrawal, reinsertion and vaginal wall repair; 5 (10.0%) patients in the first group had unintended tape removal at the time of inserter removal, necessitating the use of a second device. All of these were identified and rectified in the second group to make the procedure a safe and effective anti-incontinence procedure.

Meschia, et al evaluated the efficacy and morbidity of the TVT SECUR procedure in a prospective multicenter trial involving 95 consecutive patients. At 1 year, 91 patients were available for the analysis. The subjective and objective cure rats were 78% and 81%, respectively. These authors were particularly interested in understanding potential causes for lower cure rates compared to TVT and TVT-O. One of their assessments looked specifically at the effect of a "learning curve". Each surgeon investigator was, therefore, requested to perform at least 10 procedures before starting the formal study. And, to avoid the risk of underestimating the effectiveness of the procedure, a sub-analysis was performed where the first 10 cases for each center were removed. Analyzing the remaining 51 patients, figures were similar to those of the whole sample with 40 (78%) and 42 (82%) patients being subjectively and objectively cured.

Discussion of "U" and "Hammock" Position

Either the "U" or "Hammock" positioning of TVT Secur for incontinence treatment is an option for the surgeon, according to the instructions for use. Each option has its operative and postoperative considerations for the surgeon to assess in deciding which of these options to employ. The following experiences of direct comparison suggest, at this point in time, there is no clear preference for one over the other.

Lee, et al compared the efficacy and safety in 285 patients randomly allocated to either the "U" or "H" Hammock method of TVT-SECUR. Women with urodynamic SUI were enrolled in this 12-month multicenter randomized study. Pre and postoperative evaluations included a standing stress test, the Sandvik questionnaire, the Incontinence Quality of Life (I-QOL) questionnaire, and the International Consultation on Incontinence Questionnaire-Female Lower Urinary Tract Symptoms (ICIQ-FLUTS). Patients' satisfaction and complications were evaluated. Objective and subjective cure were defined as no leakage on the stress test and responses on the Sandvik questionnaire, respectively. One hundred forty-four (144) patients had the "U" method and 141 had the "Hammock" method. Objective cure rates were 87.5% for the "U" method and 80.1% for the "Hammock" method (p=0.091). Subjective cure rates were 77.1% for the "U" method and 75.7% for the "Hammock" method (p=0.786). Improvement in I-QOL and domain scores of the ICIQ-FLUTS (filling and incontinence sum, QOL score), and patients' satisfaction favored the "U" method. These researchers concluded both methods of TVT-S provided comparable cure rates. However, QOL and treatment satisfaction favored the "U" method.

Gagnon, et al conducted a study where the "Hammock" technique was used in the first 23 patients and the "U" method in the last 25 patients. Visual analogue scale for pain immediately and one week after surgery showed a mean score of 19/100 and 29/100, respectively. At 1 week, 2 months and 6 months after surgery, the improvement in incontinence symptoms rate was 82% (18/22), 76% (16/21), and 69% (11/16) for the "Hammock" technique, compared with 75% (18/24), 92% (22/24), and 100% (22/22) for the "U" Method. At 6 months, the difference was statistically significant (P=0.0087). These researchers concluded using the "U" method appears to be relatively safe, and the short-term efficacy rates seem to compare with traditional midurethral slings, with long-term efficacy still to be determined.

Kim, et al compared outcomes of the "U" and "Hammock" approaches of TVT Secur procedure in one hundred-fifteen (115) patients. Patients were randomly assigned to either the U or the H type approach. After 12 months, postoperative changes in the Sandvik questionnaire, incontinence quality of life questionnaire (I-QoL), Bristol female lower urinary tract symptoms-scored form (BFLUTS-SF), and postoperative patient satisfaction were evaluated. Cure was regarded as no leakage on the Sandvik questionnaire. Complications were also evaluated. Of 115 women, 53 were treated with the "U" approach and 62 women were treated with the "Hammock" approach. At 12 months, 88.7% of those treated with the "U" approach and 87.1% of those treated with the "Hammock" approach were cured (p=0.796). The I-QoL and filling, incontinence, sexual dysfunction, and QoL sum (BFLUTS-SF) scores were improved with both approaches, and there were no significant differences in the degree of improvement between approaches. Approximately 83.7% and 82.9% of the women treated with the "U" and "Hammock" approaches, respectively were satisfied with the outcome (p=0.858). Thus according to this study, the "U" and the "Hammock" type approaches of the TVT Secur procedure provided comparable effectiveness for the treatment of female SUI.

Liapis, et al assessed the efficacy and complications associated with the use of the TVT Secur device with placement of the tape in either a "Hammock" or "U" position. Of 82 patients included in the study, 43 comprised the "Hammock" group and 39 comprised the "U" group. Preoperative urodynamics results were compared with results at the 6 month and 1 year follow up. Outcome measures were objective cough test assessment and subjective patient responses to a questionnaire at follow up. The objective cure rate at 1 year follow up was 62.8% (n=27) in the "Hammock" group and 71.8% (n=82) in the "U" group. At 1 year follow up, the subjective cure, improvement and failure rates for the "Hammock" group were 60.5%, 13.9%, and 25.7%, respectively, and 69.2%, 12.8% and 17.9% respectively, for the "U" group.

Meschia, et al also concluded that there was no difference in success rate observed between the 55 "Hammock" and 40 "U" positioning included in their study.

In 2 cadaveric studies published separately in 2009 and 2010, **Hubka**, et al describe the anatomical localization of TVT Secur in the "Hammock" position and the "U" position, respectively, regarding possible injury of vessels and fixation site. TVT Secur inserters were

placed bilaterally in 14 embalmed and five fresh frozen female bodies; and 13 embalmed and five frozen fresh female bodies, respectively. In both studies, following dissection, distances from the obturator bundle were measured.

For the "Hammock" position, in embalmed bodies, the mean distance of TVT Secur from the obturator bundle was 3.05 cm. (standard deviation (SD) 0.87 cm) on the left, 2.92 cm (SD 1.24 cm) on the right. Perforation of the fascia of obturator internus muscle occurred in 38.5%. In fresh frozen bodies, results were fundamentally similar ($p>0.05$). There is a risk of injury to the obturator bundle and urinary bladder during TVT Secur. And, these researchers observed there is a significant risk of inserting the TVT Secur inserter outside the obturator internus muscle (into the lesser pelvis).

In relationship to safety and efficacy reported by the authors cited previously, this range of cure rates raises important questions about the effectiveness of mini slings in comparison to TVT and TVT-O procedures. An assessment based on direct comparisons will be addressed in the following section. However, for the above findings, the majority of the authors experienced objective cure rates of 80% or better; while 2 additional authors experienced cure rates in the high 70% range. This experience is encouraging. Nonetheless, these reports were all based on 12 month follow up. What gives rise to the question is the result reported by **Cornu**, et al based on a 30.2 month media follow up period which produced an objective cure rate of 40%. The Cornu study is relatively small, 41 patients, which in turn points to the need for larger, longer term studies to address the question of long-term efficacy.

Discussion of comparative performance of TVT SECUR relative to classic TVT and TVT-O tapes

Tommaselli, (79) et al in their 2010 article reported on 84 patients that underwent TVT-O or TVT Secur procedures. Twelve (12) months after the procedure these researchers found no differences in terms of cure rate between the two groups (81.6% vs 83.8%) and the complication rate in the TVT Secur group was lower (8.1%) than the TVT-O group (15.8%), but not significant.

Krofka, et al didn't conduct a direct comparison, but did offer a conclusion based on researched data. In a 2010 article, they report on a prospective trial involving 86 women with primary SUI. Eighty-two (82) patients had a 1 year follow up. The preoperative evaluation included urinalysis, urodynamic studies, and validated questionnaires. The 1 year outcome evaluation also included a 1-h pad testing. At the 1 year follow up, 43 (52.4%) women were objectively cured, and 14 (17.1%) women were objectively improved. These researchers concluded objective and subjective cure rates following TVT Secur are inferior to other tape procedures. However, this

method is associated with a lower incidence of perioperative and early postoperative complications.

Hinoul et al A Randomized, Controlled Trial Comparing an Innovative Single Incision Sling With an Established Transobturator Sling to Treat Female Stress Urinary Incontinence Piet Hinoul,* Harry A. M. Vervest, Jan den Boon,* Pieter L. Venema, Marielle M. Lakeman, Alfredo L. Milani* and Jan-Paul W. R. Roovers THE JOURNAL OF UROLOGY Vol. 185, 1356-1362, April 2011 performed a prospective, randomized, controlled trial in 6 teaching hospitals in Belgium and The Netherlands between 2007 and 2009. A total of 96 patients received a TVT Secur™ single incision sling and 98 received a TVT™ Obturator System. One-year followup was available for 75 single incision sling and 85 obturator system cases. Postoperative Stress urinary incontinence was objectively noted in 16.4% of the patients with a single incision sling and in 2.4% with an obturator system (p 0.05). Stress urinary incontinence was subjectively reported by 24% of single incision sling and 8% of obturator system patients (p 0.05). One year after surgery the UDI incontinence domain score in the single incision sling and obturator system groups was 21 and 13, respectively (p 0.01). Patients with a single incision sling experienced significantly less pain during the first 2 weeks after surgery (p 0.05) and returned significantly earlier to normal daily activity. Their study demonstrated that the single incision sling procedure is associated with less postoperative pain and a lower objective cure rate than the obturator system procedure.

DeBodinance, et al in their 2009 article didn't conduct a direct comparison, but did offer a conclusion based on prior research. This study evaluated the efficacy and complications of TVT Secur with a follow up of 12 months using a prospective, multicenter study of 154 patients. One hundred eighteen (118) patients were at 1 year. One hundred five (105) patients had pure stress incontinence with 12 of them presenting an intrinsic sphincter deficient. Forty nine (49) had a mixed urinary incontinence with 12 of them having ISD. The cured patients at 1 year were 70.3%, improved 11% and fails 18.7%. The cured rate did not change between 2 months and 1 year. The improved patients (24%) at 2 months remain 11% at 1 year. The recurrence rat was 12.8% at 1 year. These authors concluded the results are inferior to TVT or TVT-O procedures.

Lim, et al in their 2010 article didn't conduct a direct comparison, but did offer a conclusion based on prior experience. These authors assess objectively the success rate of the TVT Secur in the "U" configuration art six months. A prospective observational study was undertaken at two tertiary referral urogynecology centers. A cohort of 42 consecutive patients with urodynamic stress incontinence underwent the procedure in the "U" configuration. Recruitment was ceased prematurely because of a high number of early failures. Objective and subjective success rates at six months were 58.3%, respectively. On the basis of this limited study, these researchers are

hesitant to recommend the "U" configuration over its more established counterparts, the TVT and TVT-O.

Liapis, et al didn't conduct a direct comparison, but did offer conclusion based on prior published research. These authors in their 2010 article assessed the efficacy and complications associated with use of TVT Secur. This was a prospective study of patients with SUI allocated into one of two groups: "Hammock" or "U" tape placement. Of 82 patients included in the study, 43 comprised the "Hammock" group and 39 comprised the "U" group. Outcome measures were objective cough test assessment and subjective patient responses to a questionnaire at follow up. The objective cure rate at 1 year follow up was 62.8% (n=27) in the "Hammock" group and 71.8% (n=28) in the "U" group. The authors noted that efficacy of TVT Secur was lower (<72%) than the cure rates reported for other TVT procedures and concluded that further studies were required.

Meschia, et al reported didn't conduct a direct comparison, but did offer a conclusion based on comparing present results with their own previously published data on TVT and TVT-O. These researchers emphasized that a 10% drop in success rate was observed; ther4efore, they believe that TVT or TVT-O remain the reference surgical approaches.

Randomized controlled study on the TVT SECUR versus the TVT-O transobturator sling: mid term and long term outcomes; Tommaselli

3-YEAR STUDY

Randomized, single blind, controlled study conducted in two tertiary urogynecological centers. 154 patients were allocated to either TVT-O or TVT-Secur. No differences were observed in the cure rates of the 2 groups 36 months after the procedure (Table 2). Fifty seven women (86.4%) in the TVT-O group and 50 (78.1%) in the TVT-Secur group (p , .05; RR 1.1, 95% CI 0.927–1.291) were objectively cured. Subjective evaluation showed that 55 patients (79.7%) in the TVT-O group and 50 patients (74.6%) in the TVT-Secur group reported no urinary leakage (p 5 .5; RR 1.1 95% CI 0.877–1.292). In both groups, I-QOL and PGI-S scores were significantly improved at all follow-up visits. TVT-Secur seems to be noninferior to TVT-O, causes less postoperative pain, and has a low complication rate.

5-YEAR FOLLOW UP STUDY The 154 patients who were allocated to either TVT-O or TVT-Secur were contacted 5 years after the procedure to undergo urogynecological examination (POP-Q staging, challenge stress test and post-void residual urine evaluation), to complete I-QOL and PGI-I questionnaires, and to score their satisfaction on a 5-point Likert scale. Patients who were not objectively evaluated were interviewed over the telephone. Primary outcome was subjective success defined as being ‘‘very much improved’’ or ‘‘much improved’’ on the PGI-I

120 patients were evaluated only subjectively (TVT-O: 62; TVT-Secur: 58) and 84 objectively and subjectively (TVT-O: 46; TVT-Secur: 38). Subjective success (79% vs. 63.8%) and

objective cure rates (82.6% vs. 68.4%) 5 years after the procedure were lower for TVT-Secur, but not significantly. Recurrent UTIs were reported by 17.8% of women (TVT-O 9, TVT-Secur 6) and two de novo urgency cases (one per group) were observed. Re-operation rate for stress urinary incontinence (SUI) was 20%. Conclusions: TVT-Secur did not show an inferior subjective success rate in comparison with TVT-O five year after the original procedure.

Randomized controlled study on the TVT SECUR 'U' versus the TVT sling: Barber et al
Women with urodynamic stress incontinence with or without genital prolapse were randomized to receive a TVT SECUR "U" approach or TVT (N263). Those randomized to the mini-sling received two "sham" suprapubic incisions to facilitate blinding. The primary outcome was subjective cure (absence of any urinary incontinence or retreatment) as assessed at 1 year. This trial was a noninferiority study design. One year after surgery, the rate of cure was similar between treatment groups (mini-sling 55.8% compared with TVT 60.6%; mean difference, 4.8%; 95% confidence interval, 16.7 to 7.2). Incontinence severity at 1 year was greater with the minisling than with TVT (mean severity score SD: 2.2-2.7 compared with 1.5-1.7 p=0.015) resulting predominantly from a higher proportion of participants with "severe" incontinence postoperatively (16% compared with 5%; P.025). One year after surgery, 80% of individuals in the TVT SECUR "U" group and 87% of individuals in the TVT group reported that their bladder symptoms were either "much better" or "very much better" on the Patient Global Index of Improvement (P.64). Similarly, 91% of those in the TVT SECUR "U" group and 94% of those in the TVT group indicated that they would "choose the same treatment if they had to do it all over again". The mini-sling placed in the "U" position results in similar subjective cure rates to TVT 1 year after surgery but if there is a failure then the postoperative incontinence severity is greater with the TVT SECUR "U" group than with TVT.

TVT SECUR REGISTRY

Tincello et al put together a registry of women who underwent a cough stress test were treated with surgery using a single incision, retropubic or obturator sling (Gynecare® TVT SECUR™, TVT™ or TVT Obturator System, respectively) with the choice of sling based on surgeon preference. Objective cure was assessed by the standing cough stress test at 1 year. Subjective outcomes were assessed by the Incontinence Quality of Life Questionnaire and EQ-5D™

Of the 1,398 women, 32.8%, 17.8% and 49.4% received a TVT, TVT-O and TVT-SECUR, respectively. After TVT-O, fewer women had a positive cough stress test than after TVT and TVT-SECUR surgery (3.6% vs 12.8% and 15.8%, respectively). Incontinence Quality of Life Questionnaire effect size was 1.87, 1.42 and 1.56, respectively, indicating a large treatment effect. Using our Incontinence Quality of Life Questionnaire response definition 85.4%, 79.0% and 85.2% of the TVT, TVT-O and SECUR cohorts, respectively, were treatment responders (p

5 0.11).The SECUR cohort had the shortest operative time, the lowest proportion of women who required an overnight stay and the most women who underwent surgery under local anesthesia. Median time to return to employment, housework, sex life and hobbies was most rapid for SECUR. This registry demonstrated the high effectiveness of all 3 approaches. The single incision sling appeared to have objective and subjective efficacy similar to that of the retropubic sling and it can be performed under local anesthesia in an office environment.

TVT SECUR SLING UNDER LOCAL ANESTHESIA IN THE OFFICE

I performed a trial in 2012 to study 50 subjects who underwent the TVT-SECUR procedure (Hammock approach) under local anesthesia in an office setting and were followed for a period of 2 years. Retreatment for stress urinary incontinence was 9%. There was significant improvement in quality of life and symptom relief scores ($p < 0.001$). 94% percent were satisfied with the surgical outcome, and 98% felt they made the right decision. There were no intraoperative injuries or complications. Two subjects had mesh exposure in the vagina.

Discussion of complications and, or pain

Tommaselli, et al in their 2010 study showed favorable information. No intraoperative complications were observed in the two groups. The overall postoperative complications rates were 15.8% for the TVT-O group and 8.1% for the TVT Secur group (P=NS). The most frequent postoperative complications were urinary retention (two cases; 5.2%) and transient leg pain (three cases; 7.9%) for the TVT-O group and de novo urgency (two cases; 5.4%) for the TVT Secur group. One case of vaginal erosion by the tape was observed in the TVT Secur group (2.7%). Postoperative pain VAS scoring was significantly lower in the TVT Secur group in comparison with the TVT-O group, both the day after the procedure and at the first follow up visit one month after surgery ($p<0.05$). After 6 and 12 months, no patient reported pain.

In another "Hammock" versus "U" position study involving 115 patients, **Kim**, et al experienced 3 cases of intraoperative vaginal wall perforation in the "Hammock" group. Immediate postoperative retention was observed in 2 women in the "U" group and 1 woman in the "Hammock" group. One woman in the "U" group underwent tape releasing and cutting procedures for persistent large postvoid residuals.

In the largest series of "Hammock" versus "U" position comparison (285 patients) **Lee** et al experienced 3 cases of intraoperative vaginal wall perforation, 1 case of increased bleeding, and 3 cases of temporary postoperative retention.

The search also produced insight from cadaveric investigation.

Hubka, et al in their 2 cadaveric studies observed that in the "Hammock" position there is a minimal risk of injury to the obturator bundle during this procedure. However, there is a significant risk of inserting the TVT Secur inserter into the obturator fossa and NOT into the muscle. Additionally, in the "U" position they observed there is a risk of injury to the Obturator bundle and urinary bladder during TVT Secur. These observations indicate the importance of an adequately trained surgeon and clear identification of the relevant anatomical landmarks.

Overall, the experience of these researchers suggests that there are relatively few complications and that these are generally of a lower order of significance compared to those experienced with TVT and TVT-O type procedures.

META-ANALYSIS

Walsh in 2011 put together the largest review of TVT-SECUR articles published to date and found that in middle-aged women of average BMI, TVT-S is associated with both objective and subjective cure rates of 76% at 12 months. Rates of vaginal perforation (1.5%), urinary retention (2.3%), mesh exposure (2.4%) and dyspareunia (1%) appear low. The ‘U-type’ approach is associated with better objective cure rates at 12 months without an apparent increased complication rate. The rate of de novo OAB symptoms is 10% which is not lower than other MUS techniques. The primary outcomes were rates of objective and subjective cure at 12 months. For studies that divided success into ‘cure’ and ‘improvement’, only the proportion ‘cured’ was included to aid comparison across studies. 1178 published cases from 10 studies of 12-month outcomes after TVT-S procedures were included. 62% (488/784) undergoing the ‘H-type’ and 38% (296/784) undergoing the ‘U-type’ approach

A trend towards increased subjective cure amongst women undergoing the ‘U-type’ repair was found, which was not statistically significant (OR 1.41, 95% CI 0.98–2.09; P = 0.064; Table 2). The 12-month objective cure rate after a TVTS procedure, defined as negative cough stress test across all studies, was also 76% (517/ 683). Women were more likely to demonstrate objective cure after the ‘U-type’ approach compared with the ‘H-type’ approach (OR 2.2, 95% CI 1.38–3.59; P = 0.0005, Table 2). The ‘H-type’ approach conferred a significantly increased risk of vaginal perforation (2.4%)

A recent meta-analysis of surgical options for SUI showed objective cure rates at 12–18 months of 74–100% after TVT and 52–100% after transobturator tape (TOT) procedures, with most studies reporting objective cure rates of > 80% for both approaches [16]. Thus, based on a substantial body of literature, TVT-S appears to be associated with an objective cure rate lower than, but a subjective cure rate similar to, more established MUSs at 12 months.

This body of literature demonstrates that the benefits of TVT Secur outweigh the risks and that it has an acceptable safety and efficacy profile.

MY PERSONAL INVOLVEMENT WITH TVT SECUR SUBURETHRAL SLING SYSTEM

1- **AT CLINICAL TRIAL INITIATION**

In 2006, I was invited to participate in the initial pre-clinical evaluation on the TVT SECUR system. This was a cadaver course and detailed didactic session that was conducted at the Ethicon headquarters in New Jersey. The key opinion leaders with me were Drs Mickey Karram and Vincent Lucente. Mr Dan Smith, the chief project engineer, conducted the cadaver placement demonstration along with Dr Karram. We were made to place the TVT SECUR in both the U and the 'H' hammock approach and the cadaver was dissected from above to identify placement. It was confirmed that the fleece was buried into the urogenital diaphragm or the obturator internus muscle respectively.

We were made to fill out certain evaluation assessment forms and our preclinical placements were validated.

Eventually, once it was determined by the surgeons and the Ethicon TVT SECUR team that the technique in the cadaver was successfully done as per the evaluation and assessment forms, we were offered to begin a clinical trial along with Dr Dmochowski from Nashville , Dr. Nilsen from Finland, Dr. Artabani from Italy being the other investigators.

Thus, my experience with the TVT SECUR is right from preclinical stages all the way until it was withdrawn from the market.

I was part of the initial clinical trial that was a cohort study done to assess feasibility of the TVT SECUR procedure in clinical practice. This was more of a feasibility study rather than a true outcome study.

B- INITIAL EXPERIENCE-PILOT STUDY

The primary objective was to obtain clinical performance information on the GYNECARE TVT SECUR system in women with stress urinary incontinence (SUI). The primary variable for effectiveness was a >50% improvement on the subjective symptom Visual Analog Scale (VAS) assessed at Visit 3 (Day 35). Follow-up effectiveness and safety data were collected and analyzed at 6 and 12 months post-surgery. The per protocol success rate had to be at least 80% with a confidence level of 95% (lower 95% CI>80%).

This was a multicenter, open-label, randomized, non-comparative study designed to evaluate the clinical performance of the GYNECARE TVT SECUR System. The subjects were randomized to either the U or the H technique. Prior to randomization of the study population, the first 2 subjects at each site were designated “device run-in” subjects and were not to be randomized. One was given a “U” placement and the other a “Hammock” placement. Subjects were to be

evaluated preoperatively and postoperatively at Day 35, 6 and 12 months. Safety was also to be assessed over a 12 month follow-up period for all subjects.

Efficacy: The majority of subjects from both populations reported a >50% change from baseline in the primary variable, symptom VAS, on Day 35; 89.7% AND 86.7% in "U" and "Hammock" device placement groups (PP analysis set), respectively. The 95% CI for the PP success rate, when success was defined as >50% change from baseline, was 77.1% to 95.1% (Clopper-Pearson Method).

However, result from other secondary variables taken at Day 35 clearly indicate symptom and quality of life improvements in the majority of subjects. Marked improvements from baseline UDI-6 and KHQ scores were recorded, in particular in the "incontinence impact" role limitations" and "physical limitations" section. Most activities had been resumed by Day 35 with the exception of sex life (only 21.7% and 17.9% in the "U" and "Hammock" placement groups, respectively). The majority of subjects did not experience de novo urgency and only 2 subjects had undergone additional urologic/gynecological procedures prior to Day 35.

Conclusion: On self-assessment, physicians found the GYNECARE TVT SECUR device placement procedure easy to understand and perform. Most subjects did not require an overnight hospital stay after surgery and were discharged the same day with a normal voiding pattern.

The majority of subjects from both populations reported a >50% change from baseline in the primary variable, symptoms VAS, on Day 35. However, the 95% CI for the PP population success rate, when success was defined as >50% change from baseline, was less than 80% in both analysis populations (FAS and PP). Therefore, the procedures were not successful according to the criteria set out in the protocol and amendments.

The majority of adverse events were related to bladder and voiding dysfunction similar to those normally encountered with incontinence surgery. No severe or major complications occurred. The rates and nature of these complications were comparable to those reported for the general TVT device placement procedure.

The plaintiff's experts allude to the statement in this study: "As long as complications occur at the rate seen in this study and invasiveness is not very much lower than with the traditional mid urethra tension free operations, the GYNECARE TVT secure procedure cannot be recommended as a first line treatment for stress urinary incontinence".

However it should to be noted that:

1- This was a feasibility study

2- There was just one "run in" U or H case prior to the investigator-surgeons started enrollment

3- The immediate randomization to U or H technique did not allow the surgeons to get used to one technique

The plaintiff's experts state that: "51 adverse events were reported in 32 subjects during the 12 month study period". However this comment is taken out of context. None of the events were classified as severe in intensity.

The complications usually reported in literature such as mesh exposure (1 with U and 3 with H), bladder perforation (1 with U placement) were few. One case of hematoma was reported and this was managed expectantly. The other items "reported" in this study as complications were device failure, voiding dysfunction (which was transient), transient vaginal pain, urinary tract infection, device placement difficulty and recurrent stress incontinence. Most clinical trials do not categorize these as complications as they were either short-lived or due to technical errors.

As I was part of this study, I clearly remember our impression about the outcomes.

1- The procedural steps had to be diligently followed and one had to get familiarized with one type of technique U or H and master it prior to moving onto the other.

2- The learning curve is steep and requires a strict adherence to the procedural steps.

3- The procedure is vastly different from the long (TVT, TVT-O) slings and one should not get fooled by the short length of the sling or the minimal dissection or the absence of exit wounds. In fact the short sling that does not exit , itself is a major complex step and demands proper anchoring to the muscle which may not happen if due diligence is not followed.

4- The tensioning of the TVT SECUR is different and should be more snug that the retropubic TVT. If a spacer or space is left between the urethra and the sling then the failure rate is going to be very high. This aspect was hard for the surgeons to perform at this initial study as we were all used to the retropubic TVT or TVT-O style of tensioning. Only once we realized the higher failure rate that we understood the importance of sling tensioning.

In fact this study set the stage for the proper appreciation of the importance of following the IFU of the TVT SECUR. This is a procedure that has a narrow threshold for success and the procedural steps should be properly followed to avoid failures. Long term and other studies have eventually demonstrated the safety of the TVT SECUR sling and the minimal complications of the device, provided the IFU steps are followed.

C: **MIDTERM STUDY ON 141 TVT SECUR PATIENTS**

These patients were followed up for 15 months. There were no intraoperative complications. Immediate postoperative voiding function returned in all but one patient; none required sling release. Most patients (90%) reported no pain on a verbal pain scale. On follow up, 117 patients reported no SUI symptoms, 16 reported mild symptoms and eight required additional treatment. The average MESA "stress" subscore improved 79%. Eighty-five percent (85%) felt "satisfied" with the procedure. We concluded that TVT-SECUR is a safe and effective treatment for SUI.

D: **IN OFFICE TVT SECUR UNDER LOCAL ANESTHESIA: A 2 YEAR FOLOW UP**

Premise: The safety profile of the sling was evaluated by our group in over 200 cases where we did not note any complication that was major enough that would be a problem if the procedure was done in an office setting. This would include need for anesthesia, pain, bleeding, injuries to neighboring organs. We then performed 20 consecutive cases in the operating room under local anesthesia and none of them required any more anesthesia. This set the stage for doing the cases entirely under local anesthesia in the office setting.

Stringent criteria were followed for doing a surgical procedure in an office setting. In our study of 50 subjects followed up to 2 years, retreatment for stress urinary incontinence was 9%. There was significant improvement in quality of life and symptom relief scores ($p < 0.001$). 94% percent were satisfied with the surgical outcome, and 98% felt they made the right decision. There were no intraoperative injuries or complications. Two subjects had mesh exposure in the vagina.

E: **TVT REGISTRY**

Of the 1,398 women entrolled in this study, 32.8%, 17.8% and 49.4% received a TVT, TVT-O and TVT-SECUR, respectively. After TVT-O, fewer women had a positive cough stress test than after TVT and TVT-SECUR surgery (3.6% vs 12.8% and 15.8%, respectively). The SECUR cohort had the shortest operative time, the lowest proportion of women who required an overnight stay and the most women who underwent surgery under local anesthesia.. This registry demonstrated the high effectiveness of all 3 approaches. The single incision sling appeared to have objective and subjective efficacy similar to that of the retropubic sling and it can be performed under local anesthesia in an office environment.

Laser cut vs. mechanically cut TVT mesh

The initial slings that were brought out into the market were mechanically cut slings. Most of the clinical trials that have been done in the literature involve mechanically cut slings. It has been studied in over a 1000 patients and found to be clinically effective without any intrinsic defect. There was a change in the retropubic TVT design to laser cut slings. At a certain period of time both the mechanically cut and the laser cut slings were available. This was due to the fact that there were a vast number of surgeons who were happy with the mechanical cut sling and did not want to change what was working well.

Review of internal documents from Ethicon regarding the medical interpretation of biomechanical engineering test data shows no difference on the product physical characteristics

Emails received by Ethicon from individual surgeons claiming fraying of the mechanical cut slings led to the advent of the laser cut slings. The newer generation slings such as the TVT SECUR were all made as laser cut.

One of the reasons that was stated based entirely upon the internal emails of Ethicon, that I have reviewed, state that the mechanically cut slings cause fraying and possible particle loss as compared to the laser cut slings which do not have this problem.

I also reviewed the plaintiff's expert's report quoting the Ethicon emails and further stating that the mechanically cut slings lead to significant fraying, roping, curling and also particle loss.

However, this theory is not substantiated in the peer-reviewed literature, nor in my vast clinical experience.

As shown by the Ethicon engineers, the fraying of the mechanically cut sling only happens when it is subject to high stress tensions which are never encountered in a normal human body under physiological stress. Moreover, when the long slings (TVT, TVT-O) are placed, they have to be placed in a tension-free manner.

If a spacer is placed correctly between the sling and the urethra and the plastic sheaths are pulled out carefully and not vigorously, there should be no stretching of the sling. Therefore, under normal conditions of sling placement using the tension-free concept, there is no evidence of any probing, curling or fraying of the edges.

My opinion based upon reasonable degree of medical certainty, my experience doing sling procedures, review of the literature and discussion with my colleagues, is that there is no substantiated evidence that a mechanically cut sling causes more fraying and is worse than a laser cut sling.

Alternatively, I am also aware of a TVT SECUR study by Neuman (70) where he hypothesized that the sharp edge of the laser cut TVT SECUR sling could possibly increase the risk of erosion by cutting the vaginal epithelium. Plaintiffs' experts' opinions about a possible causal link between mechanically cut or laser cut causing complications are contradictory, misleading, and scientifically unreliable.

AUSTRALIAN EXPERIENCE AND TVT SECUR WITHDRAWAL

I am very familiar with the oft cited Australian experience by the plaintiff's experts. I have reviewed the product quality board presentations (PQI07-041) related to the Australian and German efficacy issue and the global complaint review data. Ethicon's analysis determined that the German and Australian experiences are different than the experiences in the United States and across the rest of the world. In fact, the Australian and German experience together accounted for 6.4% of total sales, but 91% of total complaints for post-procedure incontinence. The results of the global complaint review demonstrated that there was no safety signal with TVT Secur. In fact, only 200 TVT SECUR products were purchase in Australia with only 25 surgeons trained on the technique and only 6 surgeons had performed 10+ cases and 2 surgeons had performed 25+ cases.

This clearly is a problem of training and the learning curve that I have cited above. The TVT SECUR is a difficult procedure to master as it has to meet certain criteria as stated in the IFU. It is very easy to have missteps if these criteria are not diligently followed especially when it comes to the angle of the inserter, the insertion INTO the obturator muscle, the hugging of the back of the pubic bone etc.. In short if not done correctly there is not much leeway thereby resulting in failures.

High volume surgeons have reduced complications. In the recent Welk study, out of 59,887 women who underwent mesh based procedure for SUI, only 2.2% were treated for complications and the 10 year cumulative incidence rate was 3.29%. Welk and colleagues found that "[t]he cumulative incidence of mesh removal or revision increased from 1.2% after 1 year of follow-up to 2.5% after 10 years of follow-up. The risk of surgical revision or removal of incontinence mesh is relatively rare, but does increase with time to 2.5% after 10 years of follow-up. Patients of high volume surgeons are significantly less likely to experience complications----."

This is especially true for the TVT SECUR as the threshold for success is narrower than that for the TVT or the TVT-O procedures.

THE TVT SECUR IFU IS ADEQUATE

I have reviewed the Information of Use (IFU) of TVT SECUR and state that it is adequate. The TVT Secur IFU and Professional Education materials adequately warn pelvic floor surgeons of the risks associated with the TVT Secur device.

It is the responsibility of every surgeon to review the IFU for that particular procedural device. The IFU is written for surgeons and not for patients.

Based on my experience in doing over 300 TVT procedures, outcome analysis of this procedure by way of clinical trials, review of the medical literature that has been published on the TVT Secur, performance of the cadaver courses and Proctorship at cadaver courses and at live surgery when teaching visiting doctors or residents on performing the TVT Secur procedure, and my interaction with fellow surgeons at these events it is my opinion that the IFU for TVT Secur and Ethicon's other professional education materials like the Procedural Pearls adequately describe

the risks that are specific and/or unique to TVT Secur. Additionally, I believe that the surgical risks and complications—and not warnings about plaintiff-alleged design flaws—that plaintiffs' experts say should be included in the TVT Secur IFU are risks that are generally known to pelvic floor surgeons. These opinions are based on the following:

- Although I am not a regulatory expert, I have reviewed 21 C.F.R. 801.109(c), which permits the omission of risk information if "the article is a device for which directions, hazards, warnings, and other information are commonly known to practitioners licensed by law to use the device." Also, the FDA's "Blue Book Memo" says basically the same thing, stating that information may not be included in a warning label if "the directions, hazards, warnings, and other information are commonly known to practitioners licensed by law to use the device…"
- The body of TVT Secur medical literature that records success and complication rates associated with these devices. This literature has been discussed above.
- The FDA's 2008 and 2011 Public Health Notices, which were publically available and discussed the risks and complications associated with pelvic mesh devices such as TVT Secur.
- My education, training, and surgical experience, which I've described above. This experience also includes a large number of patients I've treated who have been implanted with slings by doctors other than myself.
- My attendance at different medical conferences and professional society meetings. This includes infomration about the performance of TVT Secur in the hands of a wide variety of pelvic floor surgeons.
- My training of other pelvic floor surgeons in treating SUI with TVT Secur. This training provides me with a venue where I have received a lot of feedback about the risks and complications associated with TVT Secur from other pelvic floor surgeons across the country.

Further, I have reviewed numerous IFUs for a significant number of products from various medical device manufacturers, and I can confirm that the warnings in Ethicon's TVT Secur IFU are adequate and consistent with other IFUs from other sling manufacturers.

The Instructions for Use (IFU) for the TVT Secur were appropriate and adequate The IFU is intended to offer information to an experienced gynecological surgeon who is already trained in the surgical treatment of stress urinary incontinence and, more specifically, TVT Secur. It cannot, and is not, intended to take the place of medical school or surgical training. The instructions are intended for general use of the product. Variations in use may occur in specific procedures due to individual technique and patient anatomy. The instructions, therefore, including listed contraindications, warnings and precautions, are intended to be read in light of prior surgical knowledge. The TVT professional education system was extensive and I personally participated and helped educate other surgeons on numerous issues such as surgical technique, placement, complications and complication management. Technical issues regarding placement were covered in numerous modalities in the curriculum, from tips and tricks to practice pointers to surgical videos to powerpoint presentations to cadaver labs to proctoring and precepting.

Claims made by the plaintiff's expert that Ethicon was required to warn surgeons that an operation in the vagina, including the TVT Secur, could result in things like pelvic pain, dyspareunia, scarring, and vaginal shape changes, all of which can be permanent, are unfounded for the reasons I've set forth above. Further, the allegation that Ethicon was required to warn surgeons that revision might be necessary, that a permanent implant may be difficult to remove and that revision might not alleviate symptoms is meritless.

All surgeons performing vaginal surgery, including the TVT Secur, are expected to be well aware of these known potential surgical complications. Ethicon identified the correct adverse events and warnings for the TVT Secur and listed them in the IFU and further they were addressed in Professional education and they were widely publicized in peer reviewed and other literature and publications as well. Data associated with the TVT Secur which was widely studied, including efficacy, complication and reoperation rates, were widely available and well known to surgeons performing vaginal surgery.

TVT PATIENT BROCHURE

I have reviewed the patient brochure and the adequacy and appropriateness of the brochure, as well as applicable marketing documents. The patient brochure is typically to facilitate a conversation with the patient and the physician. The patient brochure is not to be the sole piece of data that a patient makes her decision, but what is most critical is the discussion between the patient and the physician to discuss the physician's success rates in his/her hands with the patient's individual factors.

My opinion on the IFU is based upon reasonable degree of medical certainty, my experience in doing over 300 TVT SECUR procedures, outcome analysis of this procedure by way of clinical

trials, review of the medical literature that has been published on the TVT SECUR, performance of the cadaver courses and Proctorship at cadaver courses and at live surgery when teaching visiting doctors or residents on performing the TVT SECUR procedure.

Further, I have reviewed numerous IFUs for a significant number of products from various medical device manufacturers, and I can confirm that the warnings in Ethicon's TVT Secur IFU are adequate and consistent with other IFUs from other sling manufacturers.

The Instructions for Use (IFU) for the TVT Secur were appropriate and adequate and were not changed from the start as there was no need to change anything. The IFU is intended to offer information to an experienced gynecological surgeon who is already trained in the surgical treatment of stress urinary incontinence and, more specifically, the TVT Secur. It cannot, and is not, intended to take the place of medical school or surgical training. The IFU states that it is "not a comprehensive reference to surgical technique for correcting stress urinary incontinence." It further provides that "[o]nly physicians trained in the surgical treatment of stress urinary incontinence should use the product. The instructions are intended for general use of the product. Variations in use may occur in specific procedures due to individual technique and patient anatomy." The instructions, therefore, including listed contraindications, warnings and precautions, are intended to be read in light of prior surgical knowledge. Among other things, the IFU warned that "users should be familiar with surgical technique for urethral suspensions and should be adequately trained in the GYNECARE TVT SECUR system before using." The TVT Secur professional education system was extensive and I personally participated and helped educate other surgeons on numerous issues such as surgical technique, placement, complications and complication management. Technical issues regarding placement were covered in numerous modalities in the curriculum, from tips and tricks to practice pointers to surgical videos to powerpoint presentations to cadaver labs to proctoring and precepting.

The claim made by the plaintiff's experts that one of Ethicon's Key Opinion Leader ("KOL") Professor Frazer reported that "the IFU is fundamentally misleading" and that "tension-free, tension-less and placement with no tension are complete misnomers, is misleading and taken out of context."5

The IFU states that that the tape must be placed with "no tension under the mid-urethra" which to a pelvic surgeon means that it should be appropriately placed commensurate to the experience of the surgeon.

The IFU clearly warns of the consequences of overcorrection or under correction and essentially leaves it up to the surgeon to make the correct determination. This is a subjective matter and is handled differently by different surgeons. Some would do a cough test at fullness, some surgeons perform a Credé Maneuver whereas others do not believe in a stress test but visually make sure that the sling is a well applied to the urethra. Hence this clearly indicates that the final outcome is

based upon an individual surgeon's experience; something that the IFU cannot dictate but can only guide.

Further, the IFU warned that "as with other incontinence procedures, de novo detrusor instability may occur following a sub-urethral procedure utilizing the GYNECARE TVT SECUR system" and to minimize risk, the tape must be placed as described in the IFU. Potential adverse reactions included possible punctures or lacerations to surrounding structures. Adverse reactions also specifically listed extrusion and erosion. This section of the IFU stated, "Transitory local irritation at the wound site and a transitory foreign body response may occur. That response could result in extrusion, erosion, fistula formation or inflammation." Gynecological surgeons are trained in the risks and benefits associated with stress urinary incontinence procedures and the IFU does not have to spell them out for the surgeon. The IFU adequately and appropriately warned surgeons of the risks associated with the device.

Claims made by the plaintiff's expert that Ethicon was required to warn surgeons that an operation in the vagina, including the TVT Secur, could result in things like pelvic pain, dyspareunia, scarring, and vaginal shape changes, all of which can be permanent, are unfounded. Further, the allegation that Ethicon was required to warn surgeons that revision might be necessary, that a permanent implant may be difficult to remove and that revision might not alleviate symptoms is meritless. The incidence of dyspareunia due to the TVT SECUR sling is less than 1% as shown by robust meta-analysis done by Walsh in 2011.

All surgeons performing vaginal surgery, including surgery including the TVT Secur, are expected to be well aware of these known potential surgical complications. Ethicon identified the correct adverse events and warnings for the TVT Secur and listed them in the IFU and further they were addressed in Professional education and they were widely publicized in peer reviewed and other literature and publications as well. Data associated with the TVT Secur which was widely studied, including efficacy, complication and reoperation rates, were widely available and well known to surgeons performing vaginal surgery.

Ethicon is not required to provide professional education to physicians but chooses to do so to facilitate patient safety. Ethicon offered a multifaceted professional education program in order to provide physicians with multiple training opportunities for the safe and effective use of the TVT products, including the TVT Secur. Ethicon's professional education program does not certify physicians to perform the procedure; it simply provides a certificate of completion. Surgical education and credentialing processes are handled by other entities especially the hospital credentialing committee. It is the individual surgeon's responsibility to determine whether he or she can safely perform any stress urinary incontinence procedure. Ethicon did not mislead physicians with the documents that it provided to physicians and patients. On the contrary, Ethicon provided professional education and materials that were helpful and accurately reflected the relevant available data.

The plaintiff's expert discuss about the Australian experience and the perception that the TVT SECUR was launched too early without any proper clinical trials. A dear doctor letter was mailed in March 2008, explaining the concerns expressed by surgeons. As a result of this letter, surgeons stopped using the product and shipped their remaining stock back to Ethicon.

I am familiar with the efficacy issues that several surgeons experienced in Australia and Germany. I have reviewed the product quality board presentations (PQI07-041) related to the Australian efficacy issue and the global complaint review data. Ethicon's analysis determined that the German and Australian experiences are different than the experiences in the United States and across the rest of the world. In fact, the Australian and German efficacy 37 complaints together accounted for 6.4% of total sales, but 91% of total complaints for post-procedure incontinence. The results of the global complaint review demonstrated that there was no safety concern with TVT Secur. It was mainly a problem of efficacy. It was determined that the surgeons were inserting the TVT SECUR sling incorrectly and this was more of a technical error than an error of the device.

TVT IS NOT CYTOTOXIC AND THE MESH DOES NOT CAUSE MALIGNANCY

Despite extensive use of the polypropylene mesh in humans over decades, concerns have been raised recently about synthetic midurethral slings and a possible link with malignancy(71). These concerns are based on rodent models that demonstrated a high rate of sarcoma formation after subcutaneous implantation of polypropylene. However, further investigation suggests that the risk of malignancy may be related to the surface area and morphology of the implanted material more than to the composition of the material, when sheets of polypropylene were implanted into mice and rats. Perforated materials have been shown to have a lower risk of malignancy.

Much research has focused on the mechanism of tumor formation and has suggested that the composition of the material is not as important as the surface area and morphology of the implanted material in regards to tumor formation. This is known as the Oppenheimer effect. Others have also cautioned against extrapolating from animal studies because "such tests are rarely predictive of performance in humans. There are many examples in which animal studies are highly misleading with respect to clinical safety and efficacy in humans."

Nonetheless, further animal studies using mesh forms of polypropylene have not shown development of sarcomas. Witherspoon et al implanted polypropylene mesh into rodents and monitored the animals for 2 years based on the previously established latency period for malignancy in rodents. No sarcoma developed.

Thus far in the literature, no malignancy associated with polypropylene mesh has been reported in humans.

Tens of millions of polypropylene mesh hernia units have been sold since the 1980s. Over 3 million polypropylene midurethral slings have been sold since the mid 1990s and hundreds of thousands of transvaginal mesh units have been sold in the last 10 years. To date, no mesh site cancers have been reported. Polypropylene mesh: evidence for lack of carcinogenicity (70).

No clinical evidence exists supporting the idea that the Prolene mesh used in TVT™ and TVT-O™ is cytotoxic and causes cell death in vivo, or is associate with malignancy that causes an increase in complications or a decrease in efficacy. There are no reported cases of TVT being causally linked to any cases of cancer (70,72,73).

TVT MESH DOES NOT FRAY, CURL, ROPE NOR IS THERE PARTICLE LOSS

I have explanted portions of the TVT SECUR mesh for indication of exposure several years after its initial placement and I have not seen any migrating particles or mesh that was degraded based on an observation at surgery. If any surface cracking or alleged degradation is going to be observed, it would be misleading to suggest that one could see signs of degradation that require SEM imaging or analytical tests to visualize or confirm. In my experience with implanting and explanting TVT mesh, I have not seen loose particles, fraying, or degraded mesh.

TVT mesh is a laser cut mesh and I have seen company documents and certain published articles that refer to laser cut meshes as being stiffer which could cause more complications such as erosions, however this has never been substantiated in published literature nor have I seen in my clinical practice of over 300 cases of TVT SECUR implantations.

Additionally, plaintiffs' experts' suggestion that the TVT Secur laser cut mesh is three times stiffer than mechanically cut mesh, and therefore, is more prone to causing mesh exposures conflicts with these data. As evidenced by the data – not the theories – from the Neuman study, this logic does not carry weight since the laser cut TVT Secur group had a 0% rate of mesh exposure.

The difficulty that some surgeons have encountered while removing the inserter is more to do with the surgical technique than a defect in the product or a problem with the IFU. TVT mesh under normal physiologic conditions and stresses does not fray or stretch. However any mesh if subject to undue tension is going to stretch as it has to show some flexural mobility. So, I am aware of the plaintiff's experts showing slides of fraying of the sling mesh but the tension applied is not physiological. Moreover, even when I have gone back to do TVT SECUR sling plications for persistent incontinence, I have never see the sling get frayed.

I am aware of an Ethicon company document (74) that showed that at physiologic tensions, the mechanical and laser cut mesh behave similarly and there is no stretching or fraying. At higher tension, this may happen but this is artificial and not natural.

TVT MESH DOES NOT DEGRADE

Polypropylene is a stable and well-accepted biomaterial with a history of over five decades of

use in mesh implants. In recent years, concerns regarding implanted polypropylene degradation have been raised as a result of very high magnification SEM images that show portions of some explanted synthetic meshes with "cracked" surfaces. These surface changes were further hypothesized to lead to adverse clinical outcomes, though this is not supported by the extensive peer-reviewed literature related to polypropylene mesh repairs. Prospective studies have followed patients with implanted mid-urethral slings for 17 years and show excellent durability and safety of the procedure.

The clinical studies (such as Clave's study) plaintiffs' experts rely on to suggest in vivo degradation occurs with TVT mesh are flawed and do not confirm in vivo degradation, nor do they show an increase in clinically significant complications caused by degradation, or how much degradation is required to cause harm.

There are several experimental studies in small and large animals showing that the inflammatory response to large pore polypropylene mesh is short lived and is needed for healing. Furthermore, Clavé et al (75) could perform chemical analysis in only 32 of 84 explants,1 which is too small a sample for an appropriately powered study. Clavé et al make several statements that their analysis is unable to confirm the oxidative damage of implanted mesh leading to degradation, including, "Several hypotheses concerning the degradation of the PP are described below. None of these, particularly direct oxidation, could be confirmed in this study . . . . The [Fourier transform infrared] analysis neither confirmed nor excluded oxidation of the PP in the in vivo environment." (75)

Clavé et al stated in their paper "We did not have the opportunity to analyze vaginal implants from nonpathological situation. Therefore, prediction of normal in vivo material aging or the range of consequences in the clinical state beyond the observed samples is not possible."1 In fact, Clavé et al (75) note that despite exhaustive testing, they cannot explain their findings. They state, "Several hypotheses concerning the degradation of the PP are described. None of these, particularly direct oxidation, could be confirmed in this study."

I have also read plaintiff's experts claims that on implantation the release of hydrogen peroxide and hypochlorous acid from leukocytes continues the oxidative process started during manufacture. They go on to state that this process causes cracking in PP fibers, etc, neglecting to note that this result has not been observed in the absence of infection or erosion, as clearly stated by Clavé et al. Without any proof they state that bacteria commonly contaminate mesh and introduce "bacterial slime." Prior work reveals that even with tapes sitting in the vagina for 6 to 12 weeks in animals and humans, and even with purulent foreign body induced sinuses, only "mixed organisms" with scant growth or no growth are cultured.(76) The reason for this finding is that bacteria are immediately attacked by leukocytes and macrophages and eliminated, even in spaces less than 5 microns.(77)

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The host response to foreign body implantation, also known as the foreign body response, has generally been described to include seven interrelated and overlapping phases including: injury, protein adsorption, acute inflammation, chronic inflammation, foreign body reaction (FBR), granulation tissue formation, and encapsulation (78). This reaction is followed by the creation of collagen III, which in some weeks converts to collagen I, which covers the implanted mesh fibers.

All this is beneficial as inflammatory response impedes wound infection during the healing phase. More importantly, inflammation is a complex process and not only is critical in the initial clearing the wound of debris and necrotic/abnormal cells, but it is equally crucial for tissue remodeling and regeneration. For this reason, it is shortsighted and premature to assume that inflammation related to the implantation of a biomaterial will be associated with poor health outcomes.

TVT mesh does not undergo degradation in vivo. There is no peer-reviewed clinical literature, including randomized controlled trials, that supports the theory that TVT mesh degrades, loses particles, ropes, frays or curls in women over time, or that there are clinically significant risks of degradation. I am not aware of any peer-reviewed published literature that shows any risks or complications associated with theoretical degradation nor am I aware of any professional organizations or content experts who have expressed a concern with degradation associated with TVT mesh. Moreover, I have never seen this in my personal experience using this sling in over 300 cases spanning a period of 8 years.

TVT SECUR mesh does not undergo degradation in vivo. There is no peer-reviewed clinical literature, including randomized controlled trials, that supports the theory that TVT mesh degrades, loses particles, ropes, frays or curls in women over time, or that there are clinically significant risks of degradation. I am not aware of any peer-reviewed published literature that shows any risks or complications associated with theoretical degradation nor am I aware of any professional organizations or content experts who have expressed a concern with degradation associated with TVT SECUR. Moreover, I have never seen this in my personal experience using this sling in over 300 cases spanning a period of 8 years.

TVT SECUR MESH DOES NOT SHRINK

This has been clearly shown by Nilsson in his 17 year follow up that there was no evidence of voiding dysfunction or obstructive voiding over time. The postvoid residuals did not change. This indicates that the mesh stays as it is and does not shrink.

Also a study done by Lo et al using ultrasound assessment of the TVT sling at 3 year follow up showed that sling shrinkage does not happen.

Shrinkage is a misperception as it is the scarring of the tissue around the mesh and not the mesh itself that seems to indicate that the mesh is actually shrinking. However, the weave pattern of the macroporous mesh does not allow shrinkage.

Also shrinkage when it applies to prolapse mesh cases, is due to the fact that the prolapse has been corrected and the original distention of the vaginal epithelium from the underlying prolapse is no longer there and hence the vagina conforms to its normal shape. This gives an appearance of shrinkage of tissue.

TVT polypropelene sling: material and design

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Based on their pore size, the most frequently-used materials can be grouped into four types:

Type I: Totally macroporous prostheses, such as Atrium, Marlex, Prolene and Trelex. These prostheses contain pores larger than 75 microns, which is the required pore size for admission of macrophages, fibroblasts (fibroplasia), blood vessels (angiogenesis) and collagen fibers into the pores.

Type II: Totally microporous prostheses, such as expanded PTFE (Gore-Tex), Surgical Membrane. These prostheses contain pores that are less than 10 microns in at least one of their three dimensions.

Type III: Macroporous prosthesis with multifilamentous or microporous components, such as PTPE mesh (Teflon), braided Dacron mesh (Mersilene)

Type IV: Biomaterials with submicronic pore size, such as silastic, Cellgard (polypropylene sheeting), Preclude Pericardial membrane and Preclude Durasubstitute

Surgical infection promoted by implantation of biomaterials, such as sutures and prostheses, is caused by infiltration and proliferation of bacteria into and within the pores and interstices of these synthetic materials. When interstices or pores are less than 10 microns, in each of their three dimensions, bacteria averaging 1 micron cannot be eliminated by macrophages and neutrophilic granulocytes, which are too large to enter a 10 microns three-dimensional pore.

Contrary to Type II and III, Type I prostheses deter housing and growth of bacteria, not only by admitting macrophages, but because they allow rapid fibroplasia and angiogenesis within their sufficiently wide pores, which also prevents infiltration and growth of bacteria.

More importantly, in connection with surgical infection, the totally macroporous protheses (Type I) do not have to be removed; drainage of the infected area, followed by local wound care and antibiotics, is all that is necessary to manage the infection.

TVT slings are type I polypropelene macroporous slings and allow for the free passage of macrophages which form the basis of the foreign body reaction which is protective against infection.

In ***Polypropylene: the Standard of Mesh Materials*** A.I. Gilbert et al. (**Meshes: Benefits and Risks** Schumpelick; SpringerVerlag Berlin Heidelberg 2004) notes the following, with which I agree:

> Polypropylene mesh is produced from polypropylene. Polypropylene (PP) in its monofilament form is derived from the controlled polymerization of propylene. Propylene is derived from propane gas. It is heat-resistant up to 168.3° C. or 335° F, thereby allowing it to be sterilized without compromise. PP possesses high tensile strength and good flexibility leading to its primary medical use as a suture material. It has excellent resistance to infection.
> Medical-grade PP provokes the least foreign-body reaction due to the minimal use of catalysts and additives needed to produce it.
>
> To manufacture PPM, hooked needles are used to interlock the PP filament to form vertical and crosswise rows of loops. The crosswise rows of loops are courses. The lengthwise rows of loops are wales.

Mesh in TVT Secur

I am familiar with the size the TVT mesh, its appropriateness in the body and use for SUI, its tissue response.

The TVT mesh is a monofilament polypropylene Type 1 macroporous mesh as defined by NICE and Amid classification. This Prolene mesh provides an appropriate strength, elasticity, inflammatory response, resistance to infection, good integration that allows for a successful repair. The TVT mesh per Moalli is 1379 microns and is therefore a large pore mesh. This pore size provides plenty of room for tissue integration as seen in literature and in my practice. The strength of the mesh is necessary to provide support when the stress is placed on the urethra. In addition, moving to larger pore meshes could provide more elasticity and could likely lead to an increased result of SUI.

I have reviewed the MSDS sheets and any claims that polypropylene mesh causes sarcomas, or that mesh degrades are baseless and never seen in clinical practice.

Ultrapro is Not a Safer Alternative Design for TVT Secur:

Some plaintiffs' experts have speculated that the use of a partially absorbable mesh, such as Ultrapro or Vypro would be a safer alternative material than the TVT mesh for treating stress urinary incontinence. They rely on the Okulu et al (77) study which is not a well-powered study and did not directly compare the hand-made (mechanically cut) Ultrapro pubovaginal sling to TVT or TVT-O. These claims are without reliable scientific support.

Also, the opinion that a lighterweight mesh is a safer alternative design ignores that Ethicon tried unsuccessfully to manufacture a lighterweight mesh. This attempt suffered six failed cadaver labs and the FDA rejected it's clearance application.

TVT SECUR MESH MAINTAINS ITS MACROPOROUS CONSTRUCTION AFTER IMPLANTATION

I am aware of some reports by the plaintiff's experts that the pores of the mesh collapse due to shrinkage or stretching at the time of placement and hence do not maintain the macroporous appearance.

If the sling is placed correctly then it should be laying flat under the urethra and should not stretch. Though company documents state that the laser cut TVT SECUR mesh has some advantage in this regard, mechanical cut mesh also do well and do not stretch if placed correctly. Whenever I have gone back to either perform a sling plication or excision of an exposed mesh, I have never seen a stretched or collapsed mesh.

If the mesh is stretched this is a technical error. In fact with the TVT SECUR this is unlikely to happen as the inserter is removed by a pull back technique. With the TVT or the TVT-O procedure there is a spacer placed between the urethra and the sling during the plastic sheath removal and this ensures that the mesh is not placed under undue tension.
Moreover the mesh pores are over 1 mm and hence for the pores to collapse down to less than 10 microns means that it has been placed under an abnormal tension.

CONCLUSION

It is evident from published medical literature on TVT SECUR that the safety profile is very high and the complication risks are very low. It produces the least pain and can be done under local anesthesia with very quick recovery. There are several studies that have been published which have shown the TVT SECUR to be as effective as the TVT or the TVT-O procedures. However, there is a significant learning curve and this has led to failures that had been frequently reported in the literature.

The procedural pearls/tips and tricks were created by Ethicon to guide surgeons to understand the difference in the mechanical forces that a long sling exerts as opposed to a short sling. This is mainly influenced by the way the sling is attached and also the forces that are inherently produced when the sling placement devices are removed. We have always realized that the TVT SECUR is never too loose whereas the retropubic TVT is never too tight. Leaving a gap in between the TVT SECUR sling and the urethra as is done for the long sling procedures can lead to immediate failures. Therefore, it was not unexpected to see a significant history of failures in surgeons who did a few of these cases (as in the Australian experience) and at the beginning of

their experience (Neuman study). Once the surgeon realized that the tensioning is different and had to be appropriately adjusted, the results started getting better (our experience).

Even though the TVT SECUR is not on the market, we continue to perform single incision sling procedures and have continued to enjoyed excellent results. This is a testament to the fact that it is not about the sling design but it is about the placement and tensioning which comes with experience and once this is mastered, it is hard to go back to the long slings.

My opinions stated above are to a reasonable degree of medical certainty, and my experience and involvement with the TVT SECUR sling procedure right from its inception until it was taken off the market. I reserve the right to supplement or modify my expert opinion based on the discovery, disclosure and timely provision of new findings.

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EXHIBIT D

UNITED STATES DISTRICT COURT

SOUTHERN DISTRICT OF WEST VIRGINIA AT CHARLESTON

Master File No. 2:12-MD-02327

IN RE: ETHICON, INC., PELVIC REPAIR SYSTEM PRODUCTS LIABILITY LITIGATION

MDL 2327

JOSEPH R. GOODWIN

U.S. DISTRICT JUDGE

Nancy Smallwood, et al. v. Ethicon, Inc., et al.
Civil Action No. 2:12-cv-01662

Alvette Chase v. Ethicon, Inc., et al.
Civil Action No. 2:12-cv-01533

Margaret Schomer v. Ethicon, Inc., et al.
Civil Action No. 2:12-cv-01497

Patricia Lindberg, et al. v. Ethicon, Inc., et al.
Civil Action No. 2:12-cv-01637

THE DEPOSITION OF SALIL KHANDWALA, M.D.

JULY 8, 2016

The deposition of SALIL KHANDWALA, M.D.,
Taken at 22731 Newman Street, Suite 200,
Dearborn, Michigan,
Commencing at 9:04 a.m.,
Friday, July 8, 2016,
Before Cheryl McDowell, CSR-2662, RPR.

APPEARANCES:

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Wave III cases?
A. Not yet.
Q. Okay. So you have not billed any time with respect to Wave III cases?
A. That is correct.
Q. Is it fair to say you probably have some ongoing time that you're billing with respect to Wave I cases?
A. Could you please repeat that?
Q. Sure. With respect to -- are you doing any ongoing work with respect to Wave I?
A. Not as of now.
Q. Okay. Do you anticipate any in the future?
A. I may be amending my general report on the vaginal mesh, but that is not certain.
Q. Okay. So going through Exhibit No. 2, the third line down says invoice regarding and that is it states general report.

And that would be your general liability reports for TVT and TVT-O which is one report and TVT-S?
A. That is correct.
Q. And then your case-specific review?
A. Yes.
Q. And that would be for the files of the individual

plaintiffs that you reviewed in Wave II?

A. That's correct.

Q. And then independent medical examinations.

How many independent medical examinations have you conducted in Wave II?

A. Two.

Q. And which plaintiffs were those for?

A. Mrs. Smallwood and Chase.

Q. And then time for the last item on that list is depositions, correct?

A. I'm sorry. Yes.

Q. And that would be your time for the depositions a couple weeks ago, today, and I believe there was one, a third day scheduled for next week.

A. I'm sorry. That does not include -- today is not included in this.

Q. Okay.

A. This is just the last time that I did for the two cases.

Q. Okay. Would it also include your time to prepare for the depositions?

A. No.

Q. Okay. Does it include your time to prepare for the depositions that took place on June 24th?

A. No, just the actual depositions.
Q. Okay. Do you bill separately for your time to prepare for depositions?
A. It's part of the general report or the case-specific review, same, same rates.
Q. Okay. So would the time then be combined with that -- strike that.
Is your time preparing for depositions included in this invoice, at least with respect to the depositions that already happened?
A. Yes.
Q. Okay. And it indicates that you have spent -- I haven't totaled up the number of hours, but you have broken down your hours based on the general report of seventy-two hours, is that correct?
A. That is correct.
Q. And that's for both general reports, total for the general reports?
A. Yes, three.
Q. And just to clarify, when you say three reports, three general reports, which three general reports are you referring to?
A. Two reports of three devices, the TVT, TVT-O being one report and the second is the TVT-Secur.

Q. Okay. I just wanted to make sure we were talking about two reports.
A. Yes.
Q. Three devices but two reports.
Do you know how that time is split out between the TVT-Secur and the TVT, TVT-O report?
A. I'm not sure if it is in my breakup sheet. It could possibly be.
Q. Okay.
A. But I'm not certain.
Q. Okay. Do you have a general recollection?
A. It probably would be about, if I were to guess, it will be sixty percent for the Secur and forty percent for the TVT, TVT-O.
Q. Okay. And case-specific reviews, that looks like it was about ninety-three hours.
And that would be with respect to your preparation in case-specific reports and review of medical records for those reports?
A. Medical records, the depositions, and preparation on the case, write-up of the case and things like that.
Q. Okay. And then it says review with Mr. Walker on June 23rd, five hours.
That I presume was preparation for your

know you've been practicing for many years, Doctor, does the Reliance List contain the totality of information that you relied upon with respect to your opinions in your reports?

A. Besides my experience, yes.

Q. Okay. And have you reviewed all the items that are on the Reliance List?

A. Yes, I have.

Q. You personally or have some people assisted you?

A. No, I reviewed it myself.

MR. WALKER: I'm sorry. Assist in the compilation or the review?

MS. FLAHERTY: The review of the materials, not preparation of the list.

MR. WALKER: Okay. Object to form.

MS. FLAHERTY: Okay. That's fine.

BY MS. FLAHERTY:

Q. Do you know when you last reviewed items that are listed on the Reliance List?

A. Just about a couple of days ago when I was again reviewing for the general report.

Q. And I can't recall but I think you had on your invoice roughly how much time you have spent in preparation of the report.

Does that time -- thank you. Does that time include reviewing the materials that are on the Reliance List?

A. Yes.

Q. Okay. So the seventy-two hours listed for the general report and then there are some additional hours for the case-specific reports.

A. However, several of these papers I have already reviewed before, so I've been ongoing reviewing these articles because we publish all the time. So when you're publishing, you have to know several of these topics.

So, in fact, when I was publishing for the Exair paper, in the discussion you have to know what other prolapse studies were done. So I keep reviewing these and I keep reviewing these articles on an ongoing basis.

So several of these articles and papers I'd already reviewed, and that's why I put it in my Reliance List, and some I reviewed as preparation to the general report.

Q. Okay. Do you recall when you first started to receive materials to review with respect to your report? And I will -- I understand some of the studies you've read

so.

Have you conducted any -- strike that.

Have you ever worked for the FDA?

A. No, I have not.

Q. Have you ever done any consulting work for the FDA?

A. No, I have not.

Q. Have you ever served as a regulatory consultant?

A. No, I have not.

Q. Have you done any work commenting or helping to draft proposed regulations with the FDA?

A. No, I have not.

Q. Have you done any work advising or consulting on compliance issues with the FDA?

A. No, I have not.

Q. Okay. Do you consider yourself an expert with respect to FDA regulations?

A. No, I do not.

Q. Have you ever done any work drafting warning labels for any kind of medical product?

A. No, I have not.

Q. Okay. And so that would include no warning labels with respect to pelvic mesh products?

A. That is correct.

Q. Okay. Have you -- strike that.

Do you have -- you're not a pathologist, are you?

A. I am not.

Q. Okay. And so you don't have any certifications with respect to pathology?

A. I can see slides. As a part of gynecology residency, we do a pathology rotation. So we can see slides and understand how to read slides, but I'm not a certified pathologist.

Q. Okay. And you have not previously served as an expert specific to issues on pathology?

A. That is correct.

Q. Okay. And you are not a toxicologist, are you, Doctor?

A. I am not.

Q. Okay. And you have not previously served as an expert on issues specific to toxicology?

A. That is correct.

Q. Are you familiar with the term Device History File?

A. No, I'm not.

Q. Okay. Is it fair to say then that you have not worked on a Device History File?

A. That's correct.

Q. Okay. Are you familiar with the term DFMEA?

said that maybe by the end of December, we should finish enrollment, then I would be fine, I'd be sticking to the time lines.

So it's a very loose connection. It's not that absolutely we have to do something based upon what they want, but it's tracking what am I doing. I'm not just -- it's not that the study's stopped and we're doing nothing about it. We just want to make sure we're still continuing to maintain the time line that I had proposed.

Q. So you do have some periodic reporting obligations to the company during a study of that nature?

A. Yes.

Q. Okay. I know you have some opinions that we'll get to in a little bit with respect to porosity of mesh.

Have you conducted any studies that are specific to the porosity issues?

A. No, I have not.

Q. Have you published any peer-reviewed literature with respect to, specifically with respect to porosity of pelvic mesh?

A. No, I have not.

Q. Have you conducted any studies with respect to degradation of pelvic mesh?

A. No, I have not.
Q. And have you published any studies specific or, I'm sorry, published any articles specific to degradation of pelvic mesh?
A. No, I have not.
Q. Have you conducted any studies specific to the flexibility or stiffness of pelvic mesh?
A. No, I have not.
Q. Have you published any articles specific to flexibility or stiffness of pelvic mesh?
A. I have not specifically stated or published a paper on flexibility or as you mentioned porosity.

However, in my Prolift+M paper that I had published, I did mention about the change in the porosity and the weight that happens with the Prolift+M as it -- as part of the mesh disappears or it's absorbed which is the Monocryl component of the Prolift+M. And from the -- I believe there was some mention in the discussion about the flexibility of that, of the Prolift+M mesh that I had mentioned.

Q. Okay. Have you done -- have you published any papers that discuss the flexibility or stiffness of TVT or, actually, strike that, of an SUI product?
A. Could you explain?

Q. Sure. I'll rephrase that.

Have you done or published any articles with respect to flexibility or stiffness in a midurethral sling?

A. So if you are specifically asking whether I've done anything to see the tension strength and the measuring of the weights and things like that, I have not.

Q. Okay. Are you familiar with the phrase 510(k) submission?

A. Yes, I have.

Q. Okay. Have you participated in submissions or assembly of materials for a 510(k) submission?

A. No, I have not.

Q. And you have not authored any peer-reviewed articles with respect to 510(k) submissions?

A. That is correct.

Q. Have you ever worked on the design of pelvic mesh products?

A. Yes, I have.

Q. Okay. And in what context have you worked on the design of the products?

A. There is a modification of a particular mesh system that I made so as to eliminate a passage of a trocar, and I submitted the drawings to the company.

how long that process takes?

A. I can hold the provisional patent for a year, and we have just been extending it to see that whether I need to file the final patent or do I just give up the patent.

Q. Okay. And how many years have you held that?

A. Now it's two years.

Q. Two years.

Have you ever conducted any studies on polymers?

A. No.

Q. Have you authored any peer-reviewed articles specific to polymers?

A. No, I have not.

Q. Have you done any bench research specific to polypropylene?

A. No, I have not.

Q. Have you performed any explants or revisions of pelvic mesh products?

A. Yes, I have.

Q. Do you know approximately how many revisions or explants you've performed?

A. Anything specific or just overall?

Q. Let's start with overall, and we can break it down

from there.
A. Maybe about twenty-five.
Q. And just so we're clear, does that include what I would call a trimming that might happen in the office under a local anesthesia, or is that only a surgical procedure with general anesthesia?
A. That includes any explants, whether it's in the office or in the operating room. That includes whether the mesh was used for a sacrocolpopexy or whether it was used for a vaginal prolapse. That includes whether a sling was used for incontinence, and that's includes any possible sling or mesh, whether it is Ethicon or non-Ethicon, and that also includes suture such as Prolene suture that could be sticking into the vagina.
Q. Okay. And when you conduct those explants, do you do any sort of microscopic evaluation of the mesh that you remove?
A. I do not, but sometimes -- I am not sure if I've done that, but I may have sent it for pathology.
Q. So you send it on to somebody else to handle the pathology, is that correct?
A. If I did that, yes.
Q. Okay. Do you have a degree in epidemiology?
A. I do not.

Q. Is it fair to say you would not call yourself an expert on epidemiology?
A. Yes.
Q. Okay. Why don't we take just a five-minute break.
A. Sure.
(Off the record at 10:27 a.m.)
(Back on the record at 10:40 a.m.)
BY MS. FLAHERTY:
Q. Okay, Doctor. We're back on the record, and I want to switch gears a little bit and talk about your treatment of patients with urinary stress incontinence.
And I think you had mentioned was it roughly twenty to twenty-five percent of your patients have urinary stress incontinence, is that correct? Did I get that correct?
A. That is correct.
Q. Okay. And is it fair to say that for at least some of these patients, their incontinence is a quality of life issue for them?
A. Most patients who come to see us usually do that for that particular reason, it is bothering them, and very few would come in just because they've been sent by their physician. But most of them would come for

does not need to be removed.

The typical complaint that I have seen patients come with mesh exposure is not dyspareunia. It is either vaginal spotting or more likely it is hispareunia, meaning he, her partner, feels something in the vagina that is sharp. And then if you feel this thing and, yeah, that is what is causing it, and then we may have to take care of that exposure.

But the patient almost never feels that as a cause of dyspareunia because it's already there. Whether the epithelium under that heals or not, it doesn't remove the mesh as such. So if it has healed below it and there is no exposure whereas if it's open, that doesn't make a difference from the point of view of the patient.

Q. And you have not analyzed any of the mesh material that has been removed from women in terms of any degradation or change in consistency of that mesh from a pathologic point of view, have you?

A. I have not analyzed mesh.

Q. Okay. And you would agree that groin pain is a complication that's been reported with respect to midurethral slings, is that correct?

A. Yes.

initially set, and then as we go on, we say what did we learn from clinical experiences, what did we learn from our peers, what did we learn from what is published, and based upon that, we came up with these different notions and ideas and we put together in there what you mentioned, the Tips and Pearls.

BY MS. FLAHERTY:

Q. Okay. So it sounds like the implantation technique and the tensioning were factors with respect to the outcome for a particular patient or doctor?

MR. WALKER: Object to form.

THE WITNESS: From the point of view of the TVT-Secur, it's very important to do it correctly, and if it was -- if the procedure points that are highlighted in let's say the IFU, they're mentioned there but they had to be stressed, the value of doing this correctly.

So, for example, the IFU say not too less tensioning, not too much tensioning, you know, what does that clinically mean, so how does a doctor understand those things.

So ultimately if I'm out there, if I'm out there as a doctor who is practicing and I want to know what to do, how would I go about it is to look at what

is published, what other information comes out, and usually it is mostly I would get some publications.

And in a paper that we published, we even highlighted in the discussion the value of this pull-out technique and how the sling should be positioned as opposed to the previous slings.

BY MS. FLAHERTY:

Q. And the monograph is one of the things that would help physicians understand this and highlight the importance of this as you just mentioned?

A. Yes, one of the things.

MR. WALKER: Object to form.

BY MS. FLAHERTY:

Q. Okay. Did you assist in preparation of any of the training materials with respect to the TVT or TVT-O?

A. No, I did not.

Q. Okay. Do you need a break? It's been about another hour.

A. No. It's up to you.

MR. WALKER: Can we go off the record real quick?

MS. FLAHERTY: Yeah.

(Off the record at 11:29 a.m.)

(Back on the record at 11:38 a.m.)

Can you tell me just so I know where we're looking where in your report -- and take a minute if you need to -- your opinions are with respect to nerve damage associated with the TVT and TVT-O.

A. I do not -- the TVT and the TVT-O as a device does not cause nerve damage, so I don't think I would have a report to state that.

Q. So there's nothing in the report to state that, is that correct?

A. I do not think. I mean, I can look at it if you want, diligently look at it.

Q. I haven't seen it, so I believe you when you say that --

A. Okay.

Q. -- you don't think it's in there.

Do you have an opinion that the procedure can cause nerve damage?

A. Yes. Any surgical intervention can cause nerve damage. So whether it is an incision in the vagina or dissection can potentially cause nerve damage, or an improper placement of the device can cause nerve damage.

Q. I know we've talked a lot today about the importance of the placement and the implant technique.

You haven't rendered any opinions indicating that implanting physicians have caused or done malpractice with respect to how they've implanted mesh, have you?

MR. WALKER: Object to form.

THE WITNESS: No.

BY MS. FLAHERTY:

Q. Did you understand my question, Doctor?

A. That means have I stated that a particular doctor did something wrong.

Q. Correct.

A. No, I have not stated so, something such.

Q. And is it fair to say that if a mesh maybe has too much or too little tension that that's not a breach of the standard of care, it's a factor of the implant but not necessarily malpractice?

MR. WALKER: Object to form.

THE WITNESS: That is correct. For example, it also depends on who the patient is.

So just like what I mentioned, when I went to put a new sling in and I looked at the previous sling and I thought I could not do any better, so for most patients that sling might have done fine, but maybe this patient was a little bit obese or had a

significant cough from let's say asthma, and she may be totally different as someone else who just barely coughs. So the other barely cougher would have been just fine and the sling would have been great whereas this person, it was not tight enough for her.

So it is so subjective and has to be so much tailored to each individual patient that it's hard to determine what exactly should be the placement and the tensioning. So it is not malpractice or deviation from standard of care if it is not placed adequate for that particular patient.

BY MS. FLAHERTY:

Q. Okay. And would the same hold true with respect to the TVT-S?

A. Yes, as long as the proper steps are followed and they have done the proper procedural attachments.

For example, if they're doing it in the U fashion, then they have to put it -- the sling has to be in the urogenital diaphragm, and if it is by the H, it should penetrate the obturator internus muscle. So if that has been done, what should be done by a proper implanting surgeon, then that is standard of care.

Q. And that's information that you I think you said highlighted or stressed in the monograph --

A. Yeah.
Q. -- that you and your colleagues previously prepared?
A. That's correct.
Q. Okay. You had mentioned that any -- in your opinion surgical procedures can cause nerve damage.

Would that include the TVT-Secur implant procedure?
A. The surgical procedure, yes.
Q. Okay. Have you ever had occasion to refer a patient to another doctor for explants or revision of synthetic mesh?
A. Could you please repeat that?
Q. Sure. Have you had occasion to refer patients to other doctors for either the or for the explantation or revision of synthetic mesh?
A. I have not had, not for explants, because explant I could do it.

However, there was a patient that I had seen who was -- who came to see me because she had a sling procedure done and was complaining of pain, and I advised her that the pain was not because of the sling, and she kept insisting that I should take the sling out, and I told her that that will be not good for her because she would have incontinence, and we

that they would go to the American Urogynecology Society conference. So some of the people who are implanting slings, slings or meshes, are members of the AUGS. So I'm sure when they went to the conference, they could also do similar networking with colleagues.

BY MS. FLAHERTY:

Q. Okay. And you don't have specific information as to which doctors did or did not attend these conferences?

A. No.

Q. Do you know if Ethicon provided any training to physicians on how to remove mesh if it became necessary?

A. I don't know.

Q. Okay. And you haven't tested any mesh that you have removed from patients for degradation, have you?

A. I don't believe the mesh degrades, but I have not done any of that.

Q. So you haven't done any testing on that?

A. No.

Q. And you haven't done any testing on shrinkage or contraction of synthetic mesh, have you?

A. I have done a clinical trial in which we looked at the total vaginal length postoperatively, and if there was

put it back to where it belongs, it again reverts to its normal shape.

Very similar to what happens to the vagina after childbirth, a baby comes out the vagina, distends, but then it doesn't remain that big, it comes back to normal, and ultimately, in fact, it becomes a potential space. That means the walls are together. There is no open space in the vagina.

Similarly, once the bladder or the prolapse is put back in, the vagina goes back to its normal shape. So it's a live tissue, so it's all about the healing process.

But what we found is that there was no change. Whether there was an erosion or not, the vaginal length before and after remained unchanged, and so clinically there was no evidence of any vaginal contraction.

And that has been also reported in other not sling studies we're talking about, we're talking about mesh studies, especially with a group by Meloni, et al., were reporting.

Q. And with respect to slings specifically, you haven't done any studies on the mesh itself once it's been removed, even partially removed, in terms of shrinkage

of the mesh or any alterations to the biomechanical properties of that mesh?

A. I don't know how one can do shrinkage assessments in the lab, but biomechanical, I have not done any.

Q. Okay.

A. But the only thing as I mentioned earlier was when I have gone back and opened the vagina to see the sling during the plication procedures, I've seen that it remains the same. It has not shrunk or caused any distortion in the sling, and most of the times I see the same blue mesh as it was placed.

Q. Okay. And those plication procedures are the ones where the mesh wasn't working to stop the incontinence, and you were going in to see what was going on because it wasn't stopping -- the incontinence hadn't improved?

A. Correct.

Q. Okay. Have you conducted any studies specific to the various porosities or weight of synthetic mesh?

A. No, I have not.

Q. Okay. Is it fair to say you have not offered any peer-reviewed studies on porosity or weight of synthetic mesh?

A. That is correct.

Q. Are you aware that Ethicon has documents that discuss fraying of the TVT or TVT-O mesh?
A. I believe I read something. Maybe I don't know if it's an e-mail or something such, but I don't remember what document it was.
Q. And you haven't considered this with respect to your -- well, actually, strike that.

Have you considered that with respect to your opinions?
A. I have considered it.
Q. Okay. And it has not -- why hasn't that impacted your opinions?
A. Because in my clinical experience, I've never seen this happen. I have gone back, and even when I have seen where there's an exposure or I've opened up the vagina for the sling plications, I've seen the sling just remain as it is.

So when this is stated it could, I personally in my opinion based upon reasonable degree of medical certainty, it's based upon, you know, the surgical technique, how the sling was laid, how it was tightened, it has nothing to do with the sling itself.

So I have never seen, nor have I seen any reports of any fraying or implications of that in

clinical practice.
Q. Okay. And you've done twenty to twenty-five removal or at least explant procedures I think is how we described it?
A. Just excisions and revisions of exposures of vaginal mesh.
Q. Okay.
A. Mainly for prolapse, though.
Q. Okay. And so of that twenty to twenty-five you said mainly are prolapse, so do you have an estimate as to what percentage of those were for TVT or incontinence products?
A. I would say about maybe of that, maybe seven would be for incontinence.
Q. Okay. So with respect to the explant or revision of incontinence, synthetic incontinence mesh, you've done roughly seven or eight procedures?
A. Could you repeat that?
Q. Sure. With respect to synthetic midurethral slings and specifically the explant or revision of that mesh, have you done approximately seven or eight of those procedures?
A. Yeah. So I just want to make sure that I think explant is I'm not removing it. I've never removed a

single sling in its entirety.

Q. Okay.

A. If I've gone back, I've removed or excised the exposure in the vagina and closed the vagina on top of that.

So that's the only thing that I've encountered. I have not seen any urethral erosions or bladder erosions of the sling.

Q. And are a fair number of your patients patients that you have implanted?

A. Yes.

Q. Okay. And you haven't done any specific studies on TVT or TVT-O that other doctors have removed?

A. No.

MR. WALKER: Object to form.

BY MS. FLAHERTY:

Q. And you had testified previously that you do not have a preference of mechanical- versus laser-cut mesh?

A. That is correct.

Q. And that's because in your clinical experience, you haven't experienced a difference?

A. And also what I've seen in information published, literature prior to 2007, and if you look at literature that we just published with the TOMUS

Q. Have not?
A. Have not.
Q. Correct.
And you do not consider yourself an expert on the design of synthetic midurethral slings, do you?
A. I'm sorry.
MR. WALKER: Object to form.
THE WITNESS: Actually, I do. That's part of the reason why I'm working on this particular patent.
BY MS. FLAHERTY:
Q. Okay. And the patent, did you say that had to do with the implant technique or the mesh itself?
A. It's more the implant technique and technique itself.
Q. Do you have opinions regarding which type of implant technique is better?
A. In what sense?
Q. With respect to potential risks associated with a synthetic midurethral sling.
MR. WALKER: Object to form.
THE WITNESS: From the literature, the TVT and the TVT-O both have stood the test of time and have been studied extensively in randomized trials and

found to be very effective. So there is no doubt that the transobturator TVT-O is as good as the retropubic TVT which basically took over the gold standard pedestal from the Burch colposuspension. So we now know both these techniques are good.

However, there's some concern about the single-incision slings, but what we have realized that that's more technique driven, and now that surgeons who have mastered the technique clearly prefer the single-incision sling. I prefer the single-incision sling because I can do this entirely under local anesthesia.

It is not about the success or the complications. It is about the ease of how you can do this procedure and get the woman back into the workforce.

As you mention, transient pain can happen with any procedure. We talked about that. And with the TVT and the TVT-O, there is a potential risk of transient pain. With the TVT-Secur like products such as the single-incision sling, it is much lesser discomfort or pain, and that's what I've seen in my practice, and that's why I favor a single-incision sling.

BY MS. FLAHERTY:

Q. Okay. And with respect to the design of Ethicon's synthetic midurethral sling, you did not participate in the design of those products, is that correct?

A. That is correct.

Q. And you did not participate in the design controls with respect to those products?

A. That is correct.

Q. And do you have any knowledge regarding Ethicon's internal standards with respect to their design controls for those products?

A. Yes, I do.

Q. Okay. And what is your knowledge regarding Ethicon's standards?

A. I have read several documents that have gone over exhaustive studies for right from the Prolene suture and how it was studied to the mesh, the sling, and to the instruments, the needle that was placed for the TVT-Secur, for example, and the validation criteria that were done, the clinical trials that were done, whether it was a sheep model or ultimately the human model. So I've reviewed all that.

And on the review of the literature, my opinion is that there is extensive research and work

done in validation of the device and the instruments.

Q. So that's based on your review of literature that other people have authored?

A. Yes.

Q. And have you participated in any meetings with Ethicon regarding the design of its midurethral sling products?

A. I think, I believe by the time the TVT-Secur, when we initially started the clinical trial, the design was already established, so I was not involved in the design of the TVT-Secur.

Q. And you have not drafted or reviewed any failure analysis documents with respect to Ethicon synthetic midurethral slings, have you?

A. I have done my clinical trials. So in the clinical trials, I also mentioned the success and failures.

Q. But have you looked at any actual failure analysis documents that Ethicon has --

A. Provided me?

Q. Actually, strike that.

Have you authored or contributed to any of Ethicon's failure analysis documents?

A. No, I have not.

Q. Okay. You have not done any bench research with

respect to polypropylene, have you, Doctor?
A. No, I have not.
Q. You've not authored any studies with respect to bench research on polypropylene?
A. No, I have not.
Q. Is it your opinion that there's a learning curve with respect to the implant or the technique associated with Ethicon's midurethral slings?
MR. WALKER: Object to form.
THE WITNESS: I believe there's a learning curve with any surgical intervention. Any and every surgical intervention has a learning curve.
In fact, it's very well documented by a paper by Romans, et al., R-O-M-A-N-S, where they show that the learning curve varies depending on what is the surgical procedure and then how many years or how many months or how many procedures would it take to overcome to get to the learning curve.
BY MS. FLAHERTY:
Q. And so that would include the midurethral sling procedures as well?
A. Yes.
Q. Okay. I don't think I asked this before, and I apologize if I did. Did you draft any portion of the

IFU or Instructions For Use on the TVT?

A. I have not.

Q. And did you draft any portion of the IFU with respect to TVT-O?

A. No, I have not.

Q. And I have the same question with respect to the TVT-Secur.

A. No, I have not.

Q. Okay. Did you consult with anyone at Ethicon or did Ethicon consult with you with respect to the Instructions For Use?

A. No.

Q. Did you draft any patient brochures regarding Ethicon's midurethral slings?

A. No, I have not.

Q. Did Ethicon consult with you with respect to the patient brochures for its midurethral slings?

A. No, they did not.

Q. Do you use the patient brochures in your practice, Doctor?

A. Yes, I do.

Q. And how do you use those patient brochures?

A. It is one element of the total discussion when we do what is called a consultation visit. So we hand them

Q. And would you agree that's why it's important to have this data in the Instructions For Use so that the doctors can take the totality of that information and have that discussion with patients so patients can make an informed decision?

MR. WALKER: Object to form.

THE WITNESS: Well, the Instructions For Use is just one document. I'm not a regulatory person as I told you, so I do not know what Ethicon puts in and what they need to put in. It is just one document that we look at, and we just don't keep reviewing this again.

Information For Use is really not a document that physicians stick by and memorize. What we really memorize is what is our clinical experience and what is published in the literature and how things evolve.

As we mentioned, yes, there's a learning concern, but then we also understand what is best in my hands. So in my hands, this particular single-incision thing works great, but in Doctor Smith's hands, it may be a TVT.

So ultimately, even what the FDA states is ask your doctor what is his or her experience and